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Performance Sustainment of Two Man Crews during 87 Hours of Extended Wakefulness with Stimulants and Napping

By Patricia LeDuc
Terri Rowe
Christopher Martin
Ian Curry
Robert Wildzunas
Elmar Schmeisser
Arthur Estrada
Lisa Palacio
Tiffany Rouse
Lisa Dueringer
Lana Milam

Warfighter Performance and Health Division

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Patricia LeDuc, Terri Rowe, Christopher Martin, Ian Curry, Robert Wildzunas, Elmar Schmeisser, Arthur Estrada, Julie Bass, Lisa Palacio, Tiffany Rouse, Lisa Dueringer, and Lana Milam

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14. ABSTRACT

Thirty-two pilots each completed twenty-two simulated flights and other evaluations during 87 hours of sustained operations. General results are that dextroamphetamine and modafinil similarly attenuated numerous sleep loss problems. While caffeine had some benefits preventing performance declines, changes in performance often mimicked those seen in the placebo group. The benefits of all three stimulants were most noticeable from 0200 until 1000 when the fatigue from sleep deprivation was greatest. The most consistent drug effects were seen on physiological measures and self-reported mood, but a number of performance effects were seen as well. These data are compared to previous flight simulator studies of dexedrine and modafinil with respect to dose effects on operator performance as well as the need to examine the resilience and vulnerability of team behavior as a fatigue countermeasure. These findings strongly suggest that stimulant medications can assist the warfighter in maintaining acceptable levels of judgment and decision making, as well as crew coordination, when combat requirements dictate long periods of sleep deprivation.

15. SUBJECT TERMS

dextroamphetamine, modafinil, stimulants, extended wakefulness, sustained operations, fatigue

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Introduction

Military doctrine can require Army aviation units to operate around the clock during times of conflict. The success of military operations depends on maintaining the speed and momentum of continuous day-night operations (Department of the Army, 1997). Army personnel deployed during Operation Desert Storm confirmed the difficulties associated with operational fatigue and indicated that sleep deprivation was a problem for a number of personnel even though the actual combat period was short (Caldwell, 1992). Cornum (1992) further highlighted the problem in U.S. Air Force F-15C pilots flying air combat patrol missions during Desert Storm who suffered significant circadian rhythm disruptions and fatigue from continuous sustained operations. He further noted that effective crew rest or sleep management strategies could not have been implemented due to operational constraints.

Potential strategies for sustaining military performance in situations where sleep deprivation may be a factor include manipulating the timing and duration of sleep periods via sleep management programs or the administration of hypnotics (Babkoff & Krueger, 1992), or ensuring mandatory rest periods between missions (Department of the Army, 1988). However, these countermeasures can only work in situations where some flexibility exists in terms of personnel staffing and scheduling. During times of intense operations, administrative and behavioral interventions may not be sufficient to satisfactorily preserve performance. Even in situations where Soldiers do receive enough sleep, they may not be able to maintain appropriate levels of vigilance during long periods of overnight duty without some form of assistance. There may be times when the only viable alternative is to sustain performance with either stimulants or a combination of sleep management and stimulants.

Stimulant countermeasures

Alertness-promoting compounds are an alternative to non-pharmacological strategies when it is not possible to obtain adequate sleep because of operational constraints. Stimulants can be both convenient and effective because their utility is not dependent upon environmental manipulations or scheduling modifications. Therefore, amphetamines and other stimulants have been used extensively in military operations (Miller, 1997; Emmonson & Vanderbeek, 1993). Of the alertness-promoting compounds currently available, caffeine, dextroamphetamine, and modafinil appear to hold the most promise for use in aviation operations and have been shown to be effective in a variety of situations (Akerstedt & Ficca, 1997).

Caffeine

Caffeine (1,3,7-trimethylxanthine) is a non-regulated stimulant and among the most widely used drugs in the world (Dews, 1984a). It has been shown to have low toxicity and produces no serious adverse physiological effects (Dews, 1984b; Serafin, 1996). The stimulant effects of caffeine occur primarily via high-affinity binding to the central nervous system adenosine A1 receptor subtype, where it acts as an antagonist (Nehilg, Daval, & Debry, 1992). It is found naturally in some foods and beverages such as coffee and tea. Caffeine is also common in soft

drinks and is available in the form of over-the-counter preparations such as Vivarin® (pill), No-Doz® (pill), and Stay-Alert® (chewing gum). Caffeine is used to ameliorate the effects of sleep loss and to counteract the sleepiness associated with irregular work/rest schedules (Akerstedt & Ficca; 1997). Caffeine improves reaction time and cognitive performance, elevates mood, and reduces sleepiness (Penetar et al., 1993). Although a thorough discussion of caffeine's effects are beyond the scope of this report, research at Walter Reed Army Institute of Research indicated that doses of 200-600 mg are particularly useful for sustaining mental performance in operational settings (Committee on Military Nutrition Research, 2001). As a result, a caffeine containing gum has been placed in the active inventory. The gum, "Stay Alert," has a National Stock Number (NSN #8925-01-530-1219) and is available to all military personnel. However, caffeine has not been tested specifically as a countermeasure for sleep loss in the aviation environment.

Dextroamphetamine

Dextroamphetamine (d-alpha-methylphenthylamine) is a synthetic stimulant that has been marketed in the United States under the trade name Dexedrine® (SmithKline Beecham) since the 1960s. Dextroamphetamine is approved by the FDA for two indications: (1) treatment of the symptoms of the sleep disorder narcolepsy (excessive daytime sleepiness and uncontrollable sleep bouts); (2) treatment of the symptoms of attention-deficit disorder with hyperactivity (ADHD), including hyperactivity, distractibility, limited attention span, emotional lability, and impulsivity. The stimulant effects of dextroamphetamine occur through widespread dopaminergic (DA) action, including high-affinity binding to the DA receptor and blocking of DA reuptake. Laboratory investigations have shown that single doses (20 mg) of dextroamphetamine can return cognitive performance to baseline levels and maintain this recovery after 48 hours of total sleep deprivation (Newhouse et al., 1989). Multiple 10-mg doses of dextroamphetamine, administered prophylactically, will sustain the performance of pilots for as long as 64 hours (Caldwell et al., 1999b; Caldwell et al., 2000a). USAF EF-111A Raven jet crews were administered 5 mg dextroamphetamine during a strike on Libya in April of 1986, and were able to overcome the fatigue of the mission and the sleep deprivation that occurred in preparation for the mission (Senechal, 1988). F-15C pilots, flying lengthy combat air patrol missions during Operation Desert Shield/Storm while suffering from sleep deprivation and circadian disruption, also benefited from the use of 5 mg tablets of dextroamphetamine (Cornum, 1992).

Modafinil

Modafinil is a relatively new psychostimulant that holds promise for sustaining performance during continuous operations. Modafinil (2-((diphenyl-methyl)-sulfinyl)acetamide), a synthetic stimulant, has been available in the United States as a schedule IV drug under the trade name Provigil® (Cephalon, Inc.) since late 1998. Modafinil is approved by the FDA for treating symptoms of narcolepsy and for use in shift work disorder. Modafinil is believed to exert its stimulant effects by acting as an antagonist to the dopamine reuptake transporter. Modafinil may also act to increase the extracellular levels of dopamine (Wisor et al., 2001), although the mechanism(s) by which this occurs remain unclear. In contrast to dextroamphetamine, modafinil displays very low affinity for dopamine uptake binding sites (Mignot, Nishino, Guilleminault, &

Dement, 1994). To date, the usefulness of modafinil specifically for aviation settings has been evaluated in only two controlled aviation simulation studies (Caldwell et al., 2000b; Caldwell et al., 2004). Caldwell et al. (2000b) found that 200-mg doses (given at 2300, 0300, and 0700 during a 40-hour period of continuous wakefulness) maintained flight performance at rested levels and attenuated the effects of 40 hours of continuous wakefulness on fatigue, confusion, and physiological arousal. However, Caldwell noted vertigo, nausea, and dizziness in some subjects that were most likely the result of the dose of the medication chosen for the study. Other researchers (Buguet et al., 2003) have presented evidence to support the idea that the side effects profile of modafinil is dose dependent. Following the side effects issues raised by Caldwell, testing lower doses of the drug in an aircraft simulator was considered an appropriate step prior to in-flight tests. One objective of this research was to determine if lower doses of modafinil could maintain alertness without causing side effects that would be incompatible with flying duties or other demanding military jobs.

Napping

Unsurprisingly, taking a nap during long periods of otherwise continuous wakefulness improves alertness and performance (Akerstedt and Torsvall, 1985; Bonnet, 1990; 1991; Dinges et al., 1987; Dinges et al., 1988; Haslam, 1985; Lumley et al., 1986; Matsumoto and Harada, 1994; Naitoh and Angus, 1989; Naitoh, Englund, and Ryman, 1982; Rosa, 1993). In a study by Naitoh and colleagues (1982), subjects were given a 3-hour nap after being awake for approximately 24 hours. After the nap, they were required to stay awake an additional 20 hours. Results indicated that this 3-hour nap reduced the decline in performance during the additional work period. Other studies have found similar results using 24 hours of sleep deprivation (Dinges et al., 1987; Gillberg, 1984; Nicholson et al., 1985; Bonnet, 1990).

Nap length and placement

While nap studies vary in methodology, most studies report a dose-response relationship between the length of the nap and performance during the first 24 hours of sleep deprivation (Bonnet, 1991; Lumley et al., 1986). Many studies evaluating 1-3 hour naps have reported that alertness increases as a function of increased nap length (Naitoh et al., 1982; Lumley et al., 1986; Matsumoto, 1981). Timing of naps is also a factor affects the ease of falling asleep at various times, the quality of sleep as a function of the body's internal clock, and the subsequent effects on immediate and longer term performance. It has been established that sleep tendency is highest when core body temperature is in its trough, around 0300 (Dinges, 1986). Naps which are placed during the circadian troughs are the easiest to maintain and they show the most beneficial effects on later performance. These findings, that early morning naps are most beneficial in restoring alertness and performance, have been supported by others (Gillberg, 1984; Matsumoto, 1981; Naitoh et al., 1982).

Naps and sleep inertia

Although naps during the circadian trough may be more effective for performance sustainment, they also are the more difficult naps from which to awaken. Generally, studies have shown that post-nap sleepiness, termed "sleep inertia," is higher and performance is lower immediately upon awakening from a nap taken during the circadian trough as compared to naps taken during the circadian peak, but performance usually recovers after 15 to 30 minutes (Dinges et al., 1985). Hypnotic drugs used for nap promotion can interact with and exacerbate sleep inertia (Caldwell et al., 1997). Additionally, one study examining the use of triazolam for sleep promotion reported an instance of significant amnesia in an aviator flying a UH-60 simulator after awakening (Caldwell et al., 1996).

Nap summary

The research cited indicates that naps are beneficial for reducing sleepiness and performance decrements normally observed during sleep-deprivation periods. However, before scheduling naps during continuous operations, several guidelines can be suggested. While a nap should be as long as possible, even short naps can be beneficial. The timing of the nap should be planned in relation to the timing of work requirements. Sleep occurs most readily and performance is sustained most effectively when naps are placed in the circadian troughs, but ample time must be given for sleep inertia to dissipate following these naps. Care should be exercised before using hypnotic drugs in situations where the Soldier may need to function at maximum performance levels immediately upon awakening.

Military Issues

According to Department of the Army Field Manual No. 3-90 TACTICS 1-18, the tactician cannot ignore the human aspect of operations. He seeks to recognize and exploit indicators of fear and weakness in his enemy, and to defeat the enemy's will, since Soldiers remain key to generating combat power. More than any other human activity, continuous combat operations against an intelligent enemy take a toll on Soldiers, severely straining their physical and mental stamina. If left unchecked, these effects can result in decreased vigilance, slowed perception, inability to concentrate, communication difficulties and an inability to accomplish manual tasks.

In combat, mission demands are both intense and unpredictable, and the operational setting is not conducive to sleep even when opportunities arise. Sleep deprivation can occur simply from poor sleeping conditions, or more obviously from the requirements of continuous operations. This is a significant problem in light of the fact that it has been determined that sleep-deprived personnel lose approximately 25 percent of their ability to perform useful mental work with each 24-hour period of sleep loss (Belenky et al., 1994). Extrapolating from the research data available, by the end of a third day of sleep deprivation, Soldiers would be considered totally ineffective in the operational setting, especially in performing complex tasks (such as flying an aircraft).

Recent trends in military operations point to increases in operational tempo and a greater use of technologically sophisticated weapons systems. This may result in the need to rely on pharmacologic stimulant agents to sustain alertness. It is imperative that the relationship between sustained continuous wakefulness, pharmacological and non-pharmacological countermeasures, and their combined effects on judgment and decision-making be clearly established through scientific research. Results from this study will enable a direct comparison of the efficacy of caffeine, dextroamphetamine, and modafinil for preventing fatigue-induced performance declines in two-person aviation crews.

Information gaps

USAARL has conducted previous research on the use of stimulants to maintain aviator performance during sustained operations. In Caldwell et al. (1994; 1995), UH-60 pilots completed five, 1-hour simulator flights per day over the course of 5 days. The five day period included two 40 hour periods of wakefulness during which 10 mg of either dextroamphetamine or placebo was administered. An identical study using an actual UH-60 aircraft was published in 1997 (Caldwell et al, 1997).

In 1999, Caldwell et al. (1999b) published a similar study in which the period of wakefulness was carried out to 64 hours. In each of these studies, flight performance was maintained using dextroamphetamine and positive effects on vigor, alertness, and energy were seen in the early morning hours. Although there were minor increases in pulse and blood pressure in all of the studies, only one individual experienced an increase in diastolic pressure that approached clinical significance, and only while standing. There were no adverse behavioral effects with the exception of one subject who became excitable and talkative, but neither reckless nor dangerous as assessed by the instructor pilot. In 1999, Caldwell et al. ran a project identical to the first stimulant study (40 hrs of wakefulness) but substituted modafinil (200 mg) for the dextroamphetamine. Similar results were seen on the performance measures (1999a). There were negligible effects on temperature, pulse and blood pressure. No adverse behavioral effects were noted. As mentioned previously, vertigo, nausea, and dizziness were reported as side effects in some subjects.

USAARL research has shown dextroamphetamine (both simulated and actual flight) and modafinil (simulator only) to be effective in maintaining mood, alertness and aviation task proficiency in conditions of sustained wakefulness. Additionally, dextroamphetamine subjects showed a very low incidence of side effects, and none were judged to have been a threat to flight safety or to the aviator himself. On the other hand, some modafinil subjects in the above cited studies reported nausea, vertigo, and dizziness, all of which could pose a threat to flight safety. It remains unclear whether these potentially very serious side effects were due strictly to the higher dose of the medication used, or if it is a repeatable finding at lower doses. Finally, although caffeine is unregulated and used widely throughout the Army to combat fatigue it has not been previously examined in aviation operations.

This study's goal is to assess the effects of sustained operations and selected countermeasures (dextroamphetamine, modafinil, caffeine, and napping) on flight performance, crew-coordination, and other safety of flight issues (drug side effects, decision-making, and cognitive performance). This study emphasized the ability of two-pilot crews to maintain flight proficiency in the UH-60 simulator, and crew-coordination on an aviation related computer test. Most aviation research to date has collected data from one pilot-volunteer at a time, while few aircraft in the Army inventory are rated as single pilot aircraft.

This study compares the effects of controlled doses of caffeine (200 mg per dose) to modafinil (100 mg per dose), dextroamphetamine (5 mg per dose) and a placebo, all administered in repeated doses of 3 each at 4 hour intervals per day, one drug per volunteer across two treatment days. While modafinil and dextroamphetamine have been tested in the rotary-wing aviation environment, this study employed lower doses of these drugs than previously used in order to mitigate the side effects reported at higher dosages. Since some volunteers in USAARL's earlier modafinil study who showed clear performance benefits from the drug still reported nausea, vertigo, and dizziness while taking 200 mg per dose, we selected a lower of the modafinil for examination in this study. Likewise, a lower dose of dextroamphetamine was tested in this study as compared to 10 mg doses used in previous studies. We chose to examine this dose, since 5 mg doses have been used to good effect in actual sustained military operations (Senechal, 1988; Cornum, 1992). We have also taken this opportunity to compare data from earlier studies using 10 mg doses of dextroamphetamine and 200 mg doses of modafinil with the data collected in the present study to help determine the lowest effective dose necessary to sustain performance in aviators during extended operations.

Methods

Study volunteers

Thirty-two UH-60 rated aviators were recruited for this research (30 male, 2 female; reflecting the population ratios from which volunteers were drawn of approximately 90-95% male). The population of available volunteers included all UH-60 rated rotary wing aviators between the ages of 19 (18 if active duty) and 55. An upper limit of 55 was based on research showing that total sleep time and other sleep parameters associated with cognitive performance independent of sleep deprivation and/or drug administration can change significantly in older individuals, thus introducing a substantial source of error variance into the study. All volunteers freely gave informed consent and completed the study. Volunteers were monetarily compensated for participation in this study. All active duty military volunteers were on approved leave.

Medical

Potential subjects were excluded if they related recent daily caffeine intake exceeding 600mg, or any history of a sleep disorder. Volunteers were neither allowed to consume caffeine

during the test week nor take any medications or dietary supplements without permission from the study flight surgeon.

Study design

This study employed a double blind, repeated measures, between groups design. Two volunteers were assigned to each session until all conditions had been filled and the total number of subjects had been reached (i.e., placebo, n = 8; caffeine, n = 8; modafinil, n = 8; dextroamphetamine, n = 8). Pairs of subjects were assigned in a pseudo-random fashion to one of the drug groups. Drug administration was pseudo-randomly assigned with the constraints that (1) all drug groups were represented once before any were repeated (this qualification was used to control for potential minor seasonal effects on sleep); and (2) both volunteers participating in the same session were "blocked" together (i.e., assigned the same drug). This qualification helped to ensure double-blinding since during 68 hours of sleep deprivation it might have become obvious if one volunteer received placebo whereas the other received an active drug.

Table 1.
Testing schedule.

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<tr><th></th><th>SUN
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Day 1</th><th>MON
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Day 2</th><th>TUE
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Day 4</th><th>THU
Testing 2/
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Day 6</th><th>SAT
Recovery/
Day 7</th></tr>
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<tr><td>04:00</td><td>Testing/Dose</td><td>Testing/Dose</td><td>Wake/
Testing</td></tr>
<tr><td>05:00</td><td>Simulator</td><td>Simulator</td><td>Simulator</td></tr>
<tr><td>06:00</td><td>Wake/Shower</td><td>Wake/Shower</td><td>Shower</td><td>Shower</td><td>Shower</td></tr>
<tr><td>07:00</td><td>Meal</td><td>Meal</td><td>Meal</td><td>Meal</td><td>Meal</td><td>Wake/Shower/
Meal</td></tr>
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Hook-up/
Lab Tour</td><td>Lunch</td><td>Lunch</td><td>Lunch</td><td>Lunch</td><td>Lunch</td><td>Med Exam</td></tr>
<tr><td>13:00</td><td>Simulator</td><td>Simulator</td><td>Simulator</td><td>Simulator</td><td>Simulator</td><td rowspan="9">Release</td></tr>
<tr><td>14:00</td><td rowspan="3">Testing</td><td rowspan="3">Testing</td><td rowspan="3">Testing</td><td rowspan="3">Testing</td><td rowspan="3">Testing</td></tr>
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<tr><td>21:00</td><td>PT</td><td>PT</td><td>PT</td><td>PT</td><td>PT</td><td rowspan="3">Sleep</td></tr>
<tr><td>22:00</td><td>Sleep</td><td>Sleep</td><td>Testing</td><td>Testing</td><td>Testing</td></tr>
<tr><td>23:00</td><td></td><td></td><td></td><td></td><td></td></tr>
</table>

Procedure

Table 1 shows a list of times and activities that occurred throughout a typical week of testing. On Sunday, participants in-processed, electrodes were applied, and they completed an adaptation sleep night in the laboratory. On Monday, training/familiarity sessions were conducted at 0900, 1300, and 1700. Each training session included both the flight simulator and the computerized cognitive and reaction time tests as a block. Participants awakened at 0600 on Tuesday and began the 68-hour deprivation period. They remained awake until 0220 on Friday, when the nap was permitted. During this time period, volunteers completed 11 simulator sessions before the nap period. These were bracketed by varying numbers of computer testing episodes and physiological measurements depending on the particular test (see results). Volunteers received the opportunity for a 2-hour nap from 0220 to 0420 on Friday. They were awakened at 0420 and completed four additional test sessions (0500, 0900, 1300 and 1700). Friday night, volunteers were put to bed at 2100 for a full 10 hours of sleep. Aviators were awakened at 0700 on Saturday, given final sets of recovery tests bracketing a simulator session, underwent a medical exam, and were released at 1300.

Materials

Physiological measures

Several indices of fatigue were recorded. A pupillometer recorded pupil diameter, constriction latency, and maximum velocity during each session. Polysomnographic data were recorded and scored for sleep during (1) the baseline nocturnal sleep period, (2) objective alertness tests (RTSW, see below), (3) the 2-hour nap, and (4) the recovery sleep period.

Repeated Tests of Sustained Wakefulness (RTSW)

Subjects were required to lie on a bed in a quiet, darkened room after being instructed as follows: “lie as still as possible with your eyes closed and do your best to remain awake.” During the Repeated Test of Sustained Wakefulness (RTSW), electroencephalogram (EEG) data were recorded from electrode sites C3, C4, O1, and O2, each hemisphere’s electrodes referenced to the contralateral mastoid. The subjects were allowed to remain in bed either until 20 minutes had elapsed or until he/she entered stage 2 sleep (the first K complex or sleep spindle). The elapsed time from lights out until sleep onset was recorded.

Polysomnographic (PSG) measurements

In order to identify sleep and wakefulness, PSG were recorded (1) during the baseline nocturnal sleep period, (2) during the 2-hour nap, and (3) during the recovery sleep period. PSG measurements included EEG recorded as above and electrooculogram (EOG). Contralateral mastoid leads served as references for all measurements. All electrodes were "tin cup" style except the EOG electrodes, which were self-adhesive and worn during sleep sessions. PSG

records were divided into 30-second epochs. Each epoch was assigned a stage, consisting of wake, sleep stages 1, 2, SWS or REM. Sleep/wake scoring was conducted by a licensed sleep technician.

Vital signs

Oral temperature, blood pressure, and pulse were recorded upon arrival for the study on day 1, then every 6 hours starting at 0700 day 2. For oral temperature, the probe of an IVAC Model 4200 VitalCheck was inserted under the tongue for approximately 1 minute. For blood pressure and pulse, an IVAC Model 4200 VitalCheck was used – a blood pressure cuff was placed around the volunteer's upper arm and automatically inflated.

Questionnaires

Subjective alertness and mood was assessed using the Profile of Mood States (POMS) and the Visual Analogue Scale (VAS). Simulator sickness questionnaires (SSQ) were given after every flight. Evaluation of Risk Questionnaires (EVAR) were given once prior to drug administration and twice during the drug treatment days. Following administration of the study medications, volunteers were periodically asked whether they were experiencing a variety of symptoms commonly associated with stimulant use using the Symptom Checklist (SC). All tests were computerized for efficiency.

Profile of Mood States (POMS)

The POMS (McNair, Lorr, and Droppleman, 1992) is a 65-item adjective checklist that measured current mood states along six subscales: tension-anxiety, anger-hostility, depression-dejection, vigor-activity, fatigue-inertia, and confusion-bewilderment. Volunteers rated themselves from 1 (not at all) to 5 (extremely) for each mood-related adjective.

Visual Analog Scale (VAS)

The VAS was presented via computer and consists of eight 100-mm lines centered over the adjectives 'alert/able to concentrate', 'anxious', 'energetic', 'feel confident', 'irritable', 'jittery/nervous', 'sleepy', and 'talkative' (Penetar et al., 1993). The extremes of each line corresponded to ratings of 'not at all' on the left and 'extremely' on the right. The distance of the participant's mark from the left end of the line was scored in mm.

Simulator Sickness Questionnaire (SSQ)

After each flight, participants were asked to complete the simulator sickness questionnaire (SSQ). This questionnaire consists of 27 items, the answers to which yield scores on symptoms of nausea (gastrointestinal distress), visuomotor disturbances (eye-strain symptoms including

headache), disorientation (vestibular disturbances), and total severity of problems (overall discomfort).

Volunteers periodically completed a questionnaire listing symptoms previously reported following administration or withdrawal of dextroamphetamine, caffeine, or modafinil as well as adverse effects leading to discontinuation of the agents (PDR, 2004).

Evaluation of Risks (EVAR)

Impairments in judgment are often apparent in situations where an individual engages in behavior where the risks far outweigh the probable advantages. The propensity to engage in or avoid risky behavior and situations was assessed by a brief 24-item questionnaire that has been used to effectively measure individual variability in risk assessment in previous research with Special Operations Forces (Sicard et al., 2001). Individuals marked a point along a 100mm bipolar visual analog scale to indicate their preference for various types of risky activities. Administration time was approximately 5 minutes.

Performance tests

Vigilance was measured using an electronically-driven psychomotor vigilance task (PVT). Complex task performance requiring situation awareness was tested using the WOMBAT test system, in both single and dual person forms. Several subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) were given on a touch screen computer. This multi-dimensional test battery examines a range of cognitive functions from simple reaction time to complex executive reasoning. These tests are described below.

Psychomotor Vigilance Task (PVT)

Participants periodically completed a 10-minute PVT. A pushbutton response to the visual stimulus (presented with an inter-stimulus duration of 1-10 seconds) was required. Data consisted of simple reaction time from stimulus onset to response, number of lapses (responses greater than 500 ms), and number of anticipatory "false" responses.

Cambridge Neuropsychological Test Automated Battery (CANTAB)

The CANTAB employs touch-screen technology and rapid, non-invasive, language-independent cognitive tests. It is well validated and suitable for repeated measures testing. The following subtests were chosen based upon a review of published reports that have used CANTAB to assess stimulant effects. Specific measures extracted from these tests are given in the results section

Reaction Time (RTI). Two reaction time tasks were used: a simple single choice task and a 5-choice task. The subject touched the screen when a yellow dot was displayed. For the multiple choice reaction time task, the dot was shown in one of five locations.

Matching to Sample Visual Search (MTS). MTS was a speed/accuracy trade-off task, testing the subject's ability to match visual samples to an abstract pattern composed of four colored elements was presented in the middle of the screen. After a brief delay, a varying number of similar patterns were shown in a circle of boxes around the edge of the screen. Only one of these matches the pattern in the center of the screen and the subject had to indicate which it was by touching it. The number of patterns in the circle was 1, 2, 4 or 8, and the incorrect patterns were composed of juggled elements of the sample pattern or juggled distracter elements.

Rapid Visual Information Processing (RVP). The RVP was a test of visual sustained attention with a small working memory component. A white box was displayed in the centre of the computer screen, inside which digits, from 2 to 9, were displayed in a pseudo-random order, at the rate of 100 digits per minute. The volunteers had to detect consecutive odd or even sequences of digits (for example, 2-4-6) and respond by pressing the touch pad.

Stockings of Cambridge (SOC). This was a test of spatial planning based upon the 'Tower of London' test. The subject was shown two displays containing three colored balls. The displays could easily be perceived as stacks of colored balls held in stockings or socks suspended from a beam. This arrangement assisted subjects to come to grips with some of the rules of the problems, which involved 3-D concepts, and to fit in with the verbal instructions. The subject used the balls in the lower display to copy the pattern shown in the upper one.

WOMBAT

Performance on a complex task requiring situation awareness was tested using the WOMBAT (an acronym for "Wondrous Original Method of Basic Awareness Testing"). The test consisted of a primary flight task and three secondary tasks. The test required the participant to perceive information, allocate priorities based on new information, discover rules through induction and deduction, recognize emerging opportunities, ignore distractions, and make decisions. The Duo-WOMBAT had a dual tracking task and figure rotation, quadrant location, and digit canceling bonus tasks. The WOMBAT set-up also included two computers with monitors and consoles containing two joysticks (one with a trigger) and a 13-button keypad. The keypad consisted of 10 numeric keys (0 – 9), left and right arrow keys, and a key labeled "bonus." Performance on the WOMBAT required participants to maintain control of the tracking task (either manually or using an auto-track function) and to perform as many timed bonus tasks as often and accurately as possible. Dual portions of the task required participants to communicate with each other in order to meet the performance goals without conflicting with each other over control of test components. The program gave continuous feedback of progress toward obtaining performance goals.

Flight simulator

All flights were conducted in a NUH-60 flight simulator that included computer-generated visual displays and a multi-channel, data acquisition system for analyzing various performance

parameters for each flight. In general, maneuvers are selected based upon their complexity and the USAARL Flight Systems Branch develops a specific profile sequence of simple, average and complex flight maneuvers. The structure of the flight profile insures that the subject is stressed to varying degrees throughout the research flight period and thus allows a more sensitive analysis.

Flight evaluations for this study were performed the series of maneuvers listed in Table 2. This set of standardized visual and instrument precision maneuvers formed a flight profile designed to provide a systematic method for detecting changes in flight performance as a function both of time and the subject's alertness. During each maneuver, the subject was required to maintain control over specific flight parameters (e.g. heading, altitude, airspeed). The same sequence was used for every subject. There were 7 standardized maneuvers in the profile: one hover, one Visual Meteorological Condition (VMC) straight-and-level (SL) segment, one VMC arc requiring flying accurately around a fixed point at a fixed radius, one Instrument Meteorological Conditions (IMC) constant radius arc , one climb, and one (IMC) straight and level segment, and finally an instrument landing system (ILS) approach flown under IMC.

Table 2.
Flight maneuvers.

Maneuver	***Description***
1. Stationary Hover	Perform a 10 ft stationary hover for 2 min
2. Straight and level	Maintain VMC flight at 1500 ft, 100 KIAS for 2 min
3. Constant radius arc (VMC)	Maintain 2 mile arc, 1500 ft, and 100 KIAS for 3 min
4. Climb	Climb from 1500 to 2500 ft at 500 fpm and 100 KIAS
5. Constant radius arc (IMC)	Maintain 2 mile arc, 1500 ft, and 100 KIAS for 3 min
6. ILS Straight and level	Maintain IMC flight at 2500 ft, 100 KIAS for 2 min
7. ILS Approach	Execute ILS approach (measured from LOM to MM)

A USAARL research aviator operated the simulator and supervised all aspects of the flight from the rear of the simulator compartment, acting as air traffic control and, if needed, as crew chief. Each volunteer's objective flight performance data was collected while that individual was the pilot on the controls. The extent to which each pilot performed standard maneuvers listed above, and the correct landing sequence within established standards, was evaluated by the simulator operator. The simulator data acquisition system calculated scores for a variety of measures within each of the flight maneuvers to express how well participants maintained specific headings, altitudes, airspeeds, and other parameters (see Caldwell et al., 1994, for a detailed discussion). The duration of each flight was approximately 60 minutes (30 minutes control time per pilot). Normal conversation was not restricted between the pilots to enhance crew coordination. Mission switchover occurred following a simulated landing, and the flight profile was repeated with the second member of the pair acting as pilot on the controls for the requested maneuvers.

Results

Participants were allowed a full day of practice (day 2) on all tests (sessions 1, 2 and 3). Preliminary analyses of baseline data from the day 3 sessions (sessions 4, 5 and 6) showed that there were pre-existing treatment group differences on several of the subjective and objective test measures, despite the randomization of individuals into the treatment groups. To account for these pre-existing differences, data were transformed to baseline corrected scores for each individual as follows: the measures collected on the baseline day (day 3, prior to any drug administration or sleep deprivation) were averaged for each test by individual. This score was subtracted from that volunteer's test scores during the experimental period to remove the pre-existing pre-treatment group biases and to transform many of the data into a normal distribution, thus permitting the use of parametric statistics. The two drug administration test days' baseline corrected scores were subjected to repeated measures ANOVAs using the between-subjects factor, drug group, with four levels (caffeine, dextroamphetamine, modafinil and placebo), and one within-subject factor, test time point (labeled session, 2-14 levels, depending on the particular test). In addition, the effects of napping and a full night's sleep were analyzed by comparing performance during the immediate pre-nap session to post-nap performance (day 6), and again during recovery (day 7) after 10 hrs of restorative sleep. These conventions are shown schematically in figure 1. Note that the first 6 test iterations listed in Table 1 (Days 1 – 3) are not graphed, so the normalization by the averaged data from day 3 will not result in an overlap of the first point shown across treatments (first session on day 4).

Note that dextroamphetamine data is labeled as Dexedrine™ in report figures.

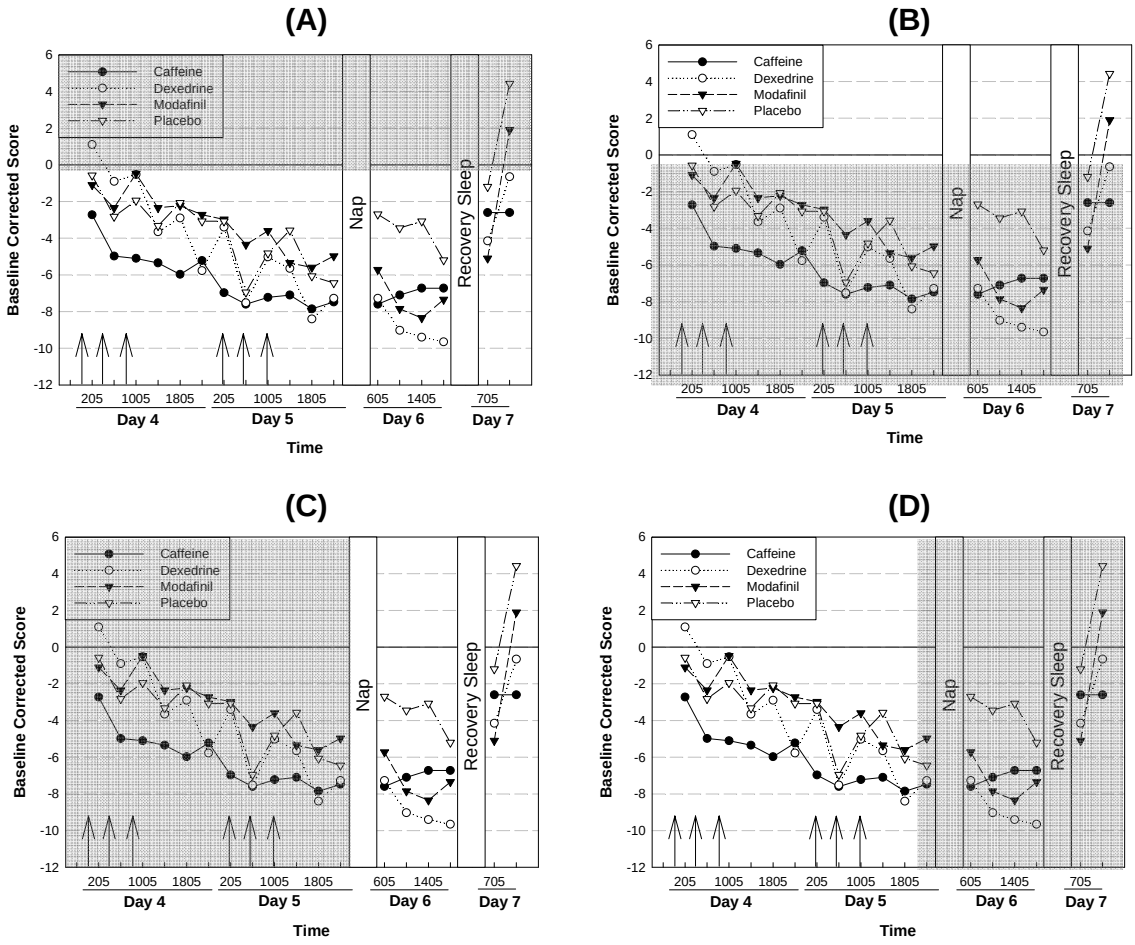

Figure 1. Schematic representation of the data conventions using the Profile of Mood States – Vigor questionnaire results as an example (figure 8D, below). Each data point represents a single test result starting at day 4; each arrow indicates the administration of a drug or placebo treatment. (A) The gray area represents the region of performance better than baseline determined by the three sessions on day 3. (B) The gray area represents region of performance worse than baseline. (C) The gray area represents Analysis A, showing the effects of drugs with sustained wakefulness. These data were collected over the first two test days and correspond to 18-60 hours since last sleep. (D) The gray area represents Analysis B, showing the effects of napping and restorative sleep on performance. The first data point corresponds to the pre-nap performance with 60 hours of sleep deprivation; the following points after the labeled break in the graph correspond to performance on day 6 after a 2-hour nap; the final points after the second labeled break correspond to performance on the recovery day, day 7, after a 10-hour period of restorative sleep.

Main effects for session were seen on most of the normalized variables measured in this study. While these findings are unremarkable unto themselves given the length of sleep deprivation used in this study, they do illustrate the ability of these particular tests to detect changes in performance. These tests appear to capture performance differences produced by sleep loss as

evidenced by the changes detected across sessions. Additionally, these tests appear to be sensitive enough to pick up performance differences produced by circadian variations. As such, session effects will be discussed only if they occur in a 2-way interaction involving drug group. In the results paragraphs that follow, for each data set the initial section is limited to the baseline corrected data of day 4 and day 5 (Analysis A); the second section is limited to the data from the last data point before the nap through the end of the study on Day 7 (Analysis B).

Physiological measures

Pupillometry

Ocular changes assessed with the pupillometer demonstrated a drug main effect on both minimum pupil diameter ($F(3, 28) = 8.804$, $p<0.000$), and maximum pupil diameter ($F(3, 28) = 7.225$, $p<0.001$) (figure 2, data from day 4 and 5 only). Post hoc analyses showed that maximum pupil diameter was significantly higher in the dextroamphetamine group than in the placebo and caffeine groups ($p<.05$). Likewise, the minimum pupil diameter was significantly higher in the dextroamphetamine and modafinil groups than in the placebo group ($p<.05$) and the dextroamphetamine group's minimum was significantly greater than the caffeine group ($p<.05$). Neither session effects, nor session × drug group interactions were significant for any of the measures.

The pupillometry data from the separate nap/sleep analysis (days 6 and 7 data only) showed no significant main effect for drug group. Only the minimum pupil diameter changed significantly over session ($F(6, 168) = 3.780$, $p<0.002$), but none of the session × drug group interaction effects were significant.

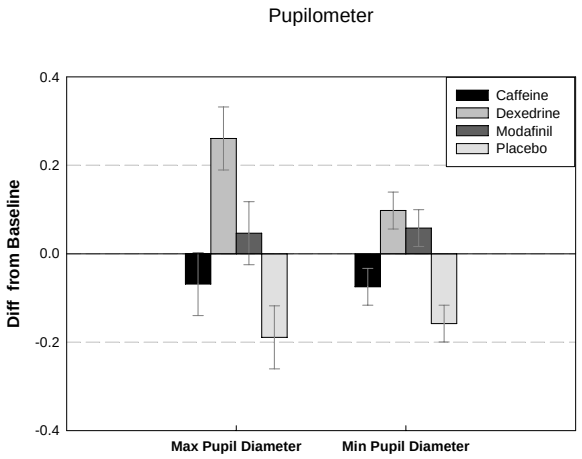

Figure 2. Pupil minimum and maximum diameters by drug group ($p<0.05$).

Vital Signs

Vital sign measurements included oral (T)emperature, (S)ystolic and (D)iastolic blood pressure, and heart rate (HR). These data were recorded upon arrival for the study on day 1, then every 6 hours starting at 0700 day 2. Analyses of these data revealed no significant differences among drug groups on any of the measures except heart rate ($F(3, 28) = 13.996$, $p<0.000$). The post-hoc analysis revealed that this was due to a significantly elevated pulse rate in the dextroamphetamine and modafinil groups as compared to the placebo and caffeine groups.

There were significant main effects measures during the sleep deprivation segment for session for all except diastolic blood pressure, T ($F(15, 420) = 17.228$, $p<0.000$), S ($F(15, 420) = 2.156$, $p<0.007$), HR ($F(15, 420) = 8.883$, $p<0.000$) indicating normal circadian fluctuations (figure 3). Additionally, there were significant session × drug interactions for temperature and diastolic blood pressure; T ($F(45,420) = 1.577$, $p<0.017$), D ($F(45, 420) = 1.739$, $p<0.010$). The post hoc analysis on temperature was unremarkable (figure 3A), but diastolic blood pressure analysis indicated that the significant differences were due to highly variable fluctuations across sessions in the caffeine group relative to other three groups (figure 3D).

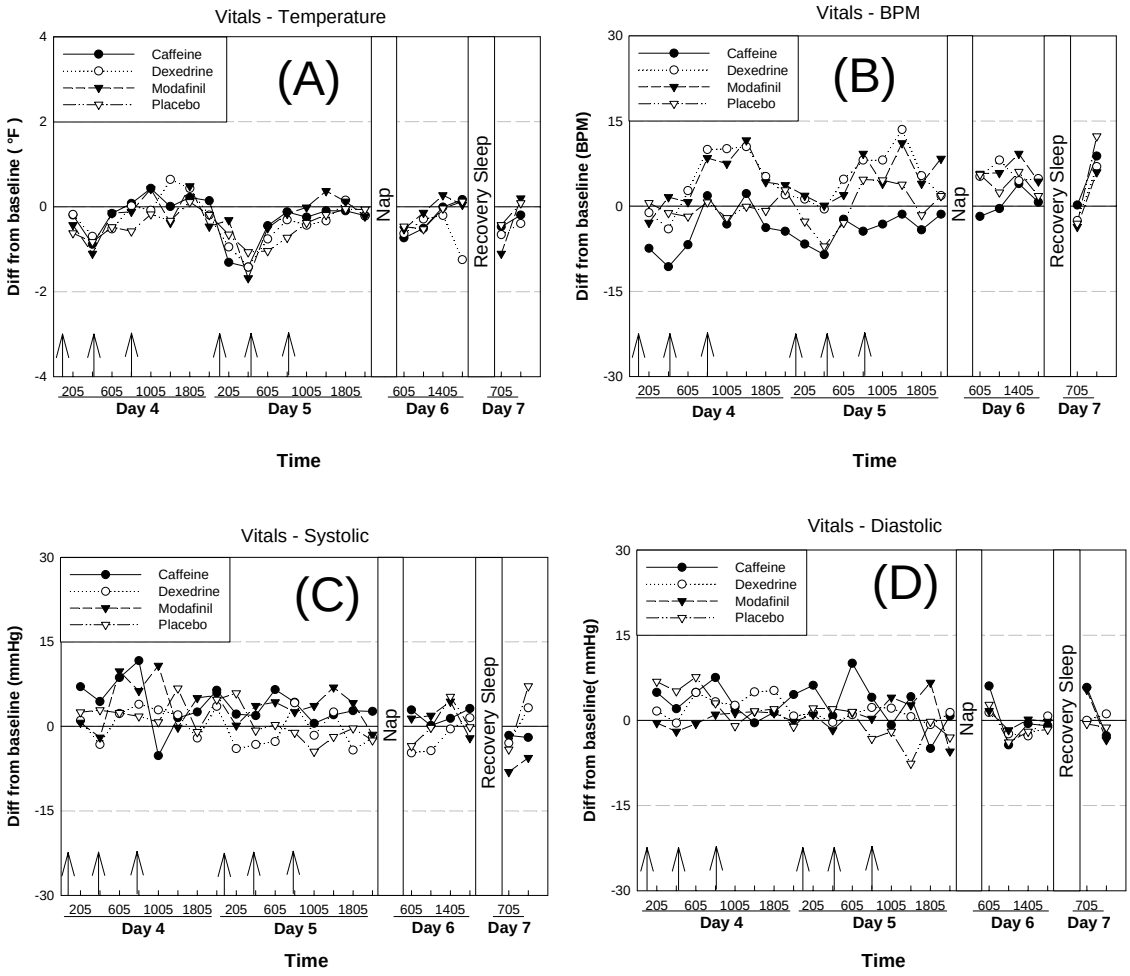

Figure 3. Changes in vital sign data across test sessions: (A) temperature in ^{o}F, (B) heart rate beats/min, (C) diastolic blood pressure in mm Hg, and (D) systolic blood pressure in mm Hg.

The nap/sleep analysis indicated no significant main effect for drug groups across the vital signs measured. Significant differences across sessions indicated normal fluctuations typical of circadian variation, T ($F(6, 168) = 4.175$, $p<0.001$), D ($F(6, 168) = 3.810$, $p<0.001$), P ($F(6, 168) = 8.788$, $p<0.000$), however, no significant differences in the session × drug group interactions were found.

Repeated Test of Sustained Wakefulness (RTSW)

During the RTSW the elapsed time from lights out until sleep onset was recorded. Analysis of variance of the sleep deprivation segment data showed that there was a significant main effect of drug group on the amount of time required to reach stage 2 sleep ($F(3, 28) = 3.127$, $p<0.042$). A Tukey HSD post hoc analysis showed that this was due to the placebo group entering stage 2 sleep significantly faster than the dextroamphetamine group. Additionally, there was a significant session effect ($F(5, 140) = 18.020$, $p<0.000$), but there were no interaction effects

between drug group and session. A post hoc test for session revealed that the significant differences were due to steady declines in time to reach stage 2 sleep as function of sleep loss.

The 2-hour nap did not significantly affect the time to reach stage 2 sleep among drug groups, but a session effect indicated the 10-hour recovery sleep returned RTSW to pre-sleep deprivation levels ($F(3, 84) = 37.414$, $p<0.000$). The session × drug group interaction on the nap/sleep period data was not significant (figure 4).

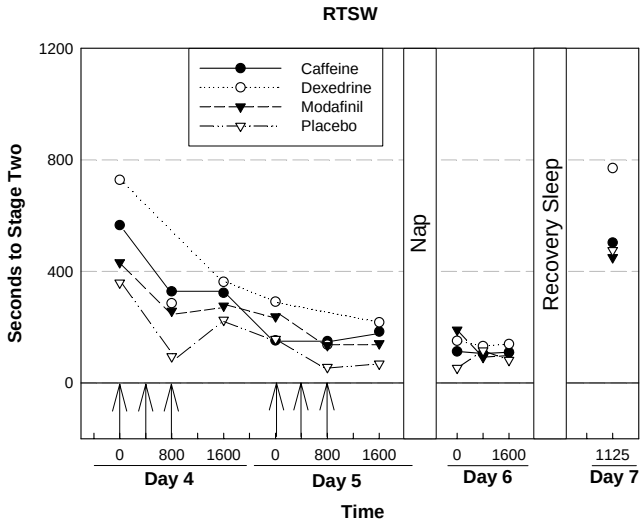

Figure 4. RTSW raw (non-normalized) data. Shows the amount of time, in seconds, required to enter stage 2 sleep by group across all sessions.

Polysomnography (PSG)

Nap Effects. A 2-hour nap was provided to determine its effects on restoring performance. During this nap, PSG data were recorded to determine the amount and quality of each stage of sleep (figure 5). Note, since there was only one nap period, these data are expressed in minutes and not as change from baseline. An analysis of these data revealed no differences among drug groups in Stage 1 or Stage 2 sleep. However, there were significant differences among drug group effects on slow wave sleep (SWS) ($F(3, 28) = 3.159$, $p<0.040$) and REM (rapid eye movement) ($F(3, 28) = 2.923$, $p<0.050$) stages of sleep. Post hoc analysis identified differences in sleep were due to dextroamphetamine group spending more time in SWS than the modafinil group; while the converse was true for REM sleep – the modafinil group's time in REM was significantly greater than the dextroamphetamine group.

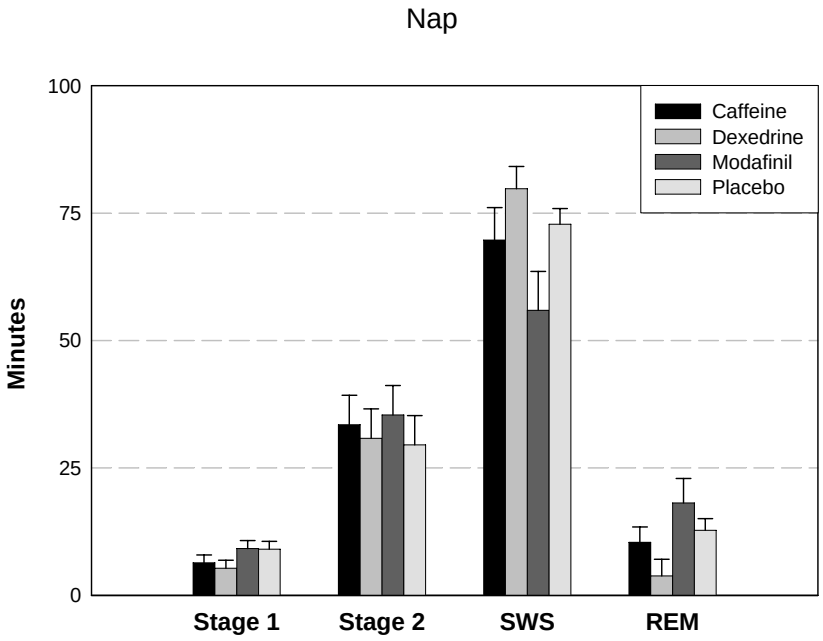

Figure 5. Time spent in each stage of sleep during the 2-hour nap.

Recovery sleep. Sleep quality during the 10-hour sleep recovery period was recorded and compared to baseline PSG patterns. Because the baseline sleep period was only 8-hours, these data were computed as the percentage of time spent in each stage of sleep and then expressed as change from this baseline. This analysis showed that no drug differences were apparent in the percentage of time spent in Stage 1 sleep, Stage 2 sleep, or SWS. There were, however, significant differences among drug groups in the percentage of time spent in REM sleep ($F(3, 28) = 3.141$, $p<0.041$). Post hoc analyses indicated that placebo group spent significantly more time in REM sleep than the caffeine group (figure 6).

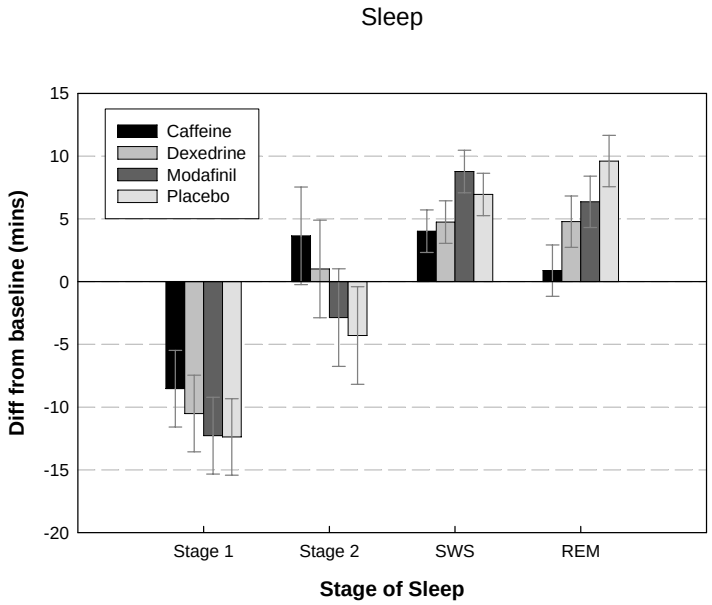

Figure 6. Time spent in each stage of sleep during recovery sleep.

Questionnaires

Profile of Mood States (POMS)

Baseline corrected data for the POMS were measured across six independent subscales: (T)ension-anxiety, (A)nger-hostility, (D)epression-dejection, (V)igor-activity, (F)atigue-inertia, and (C)onfusion-bewilderment. Volunteers rated themselves from 1 (not at all) to 5 (extremely) for each mood-related adjective. An analysis of variance revealed a main effect for drug only on the fatigue subscale ($F(3, 28) = 4.283$, $p< 0.013$). A Tukey's HSD (honest significant difference) post hoc comparison indicated that this difference was due to significantly lower reports of fatigue by the dextroamphetamine group than by the placebo group (collapsed across all sessions in days 3 and 4). These data are shown in figure 7. No main effects were found for drug on the scales. Significant main effects for session were seen on all the subscales except anger, as follows: T ($F(11, 308) = 4.790$, $p< 0.000$), D ($F(11, 308) = 2.49$, $p< 0.028$), V ($F(11, 308) = 15.302$, $p< 0.000$), F ($F(11, 308) = 24.842$, $p< 0.000$) , and C ($F(11, 308) = 6.763$, $p< 0.000$),

however, no interactions between drug and session achieved significance. These data are shown in figure 8.

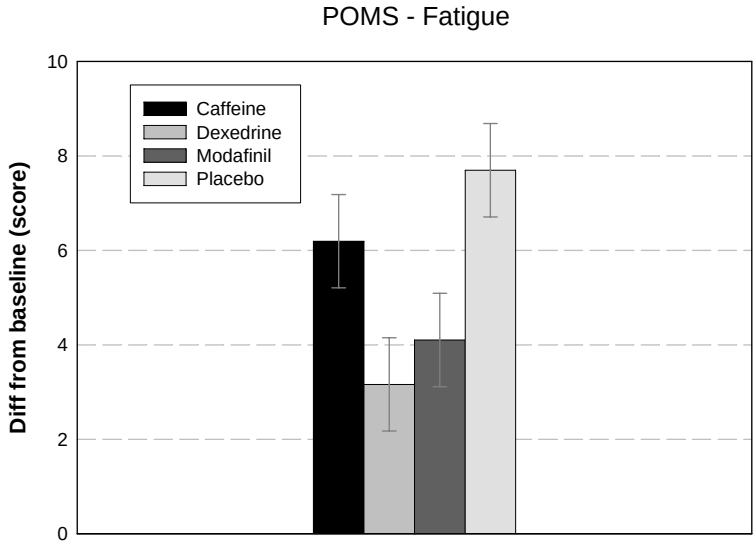

Figure 7. POMS fatigue scale. Mean differences from baseline score show a significant main effect among drug groups; dextroamphetamine < placebo (p<0.05).

A separate analysis of variance (Analysis B) was performed to determine the effects of a 2 hour nap and 10 hours of restorative sleep on mood. There were no main effects due to drug (nor were they expected 18 hrs after the last dosing, since by then most of the drug had been eliminated). Again session effects were found for most subscales; T (F(6, 168) = 11.751, p< 0.000), V (F(6, 168) = 22.640, p< 0.000), F (F(6, 168) = 45.118, p< 0.000), and C (F(6, 168) = 15.607, p< 0.000). Drug × session interactions achieved significance only for the fatigue and depression subscales; D (F(18, 168) = 2.059, p< 0.017), F (F(18, 168) = 3.069, p< 0.000). The Tukey HSD comparison showed that for the fatigue subscale, the modafinil group reports were significantly higher than the placebo group during the session 4 hrs post nap. By 8 hrs post nap, fatigue in the modafinil and dextroamphetamine groups was significantly higher than placebo, and modafinil also was significantly higher than caffeine. After 10 hours of restorative sleep, the reported fatigue was greater for the caffeine group than both the dextroamphetamine and placebo groups. Just prior to release of the participants, the caffeine group still was reporting higher fatigue than the placebo group (figure 8E). Additionally, during the pre-nap session, depression symptoms for both the modafinil and dextroamphetamine groups were significantly lower than placebo. Likewise, a spike in the depressive symptoms for the caffeine group, post nap, resulted in their scores being significantly higher upon awakening than for the dextroamphetamine group (figure 8C).

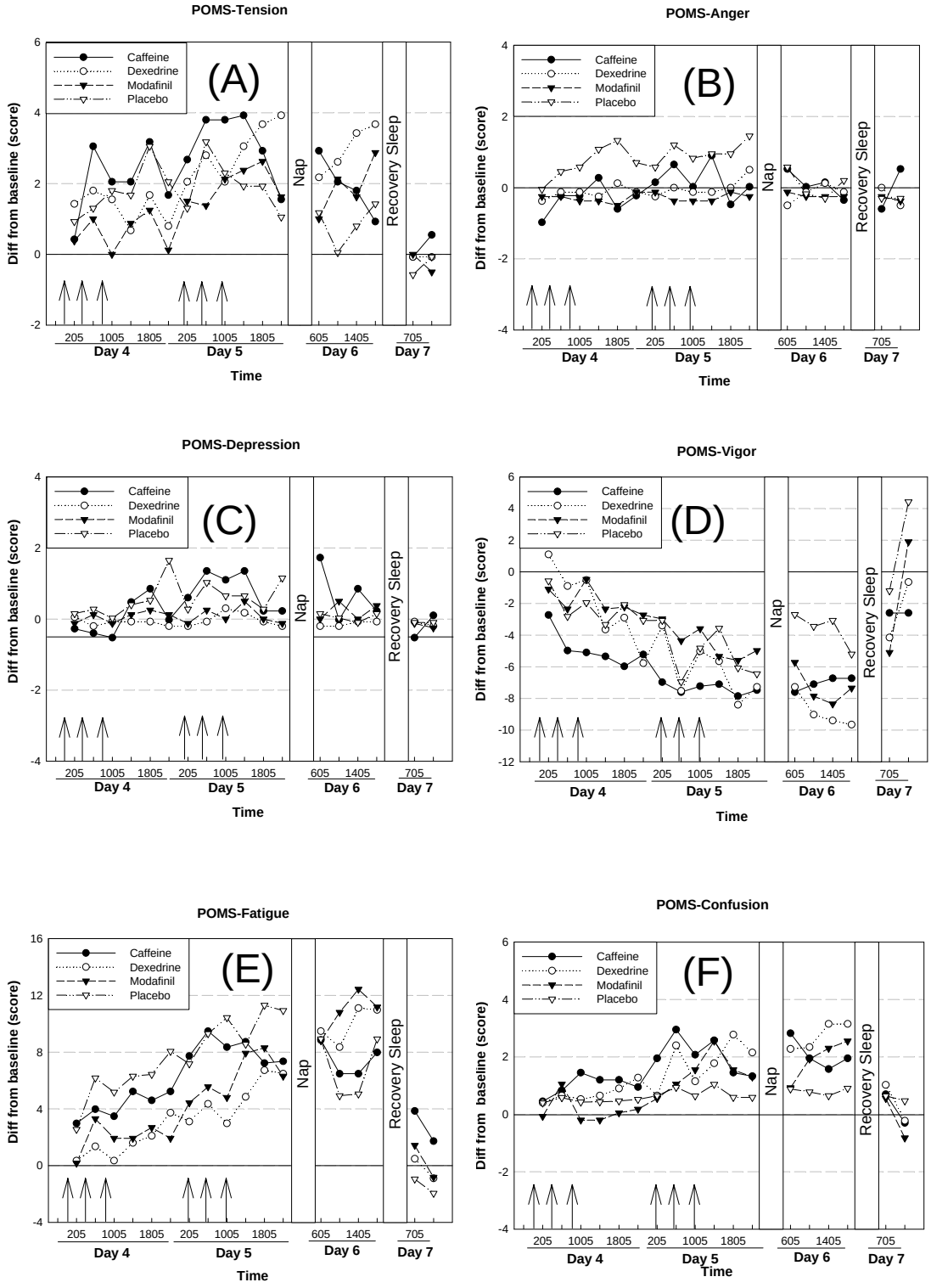

Figure 8. POMS data for the six subscales across all test sessions: (A) Tension, (B) Anger, (C) Depression, (D) Vigor, (E) Fatigue, and (F) Confusion.

Visual Analog Scale (VAS)

On the VAS, significant drug main effects were reported among the groups for (Al)ertness ($F(3, 28) = 4.731$, $p<.009$), (I)rritability ($F(3, 28) = 3.051$, $p<.045$), (S)leepiness ($F(3, 28) = 3.361$, $p<.033$), and (T)alkativeness ($F(3, 28) = 4.506$, $p< 0.011$). Significant drug main effects were absent from the rest of the VAS scales. Tukey's HSD indicated that the modafinil and dextroamphetamine groups reported significantly higher alertness than the placebo group; that the dextroamphetamine group reported significantly less irritability and sleepiness than the placebo group; and, that the caffeine group reported significantly less talkativeness than the modafinil group (figure 9).

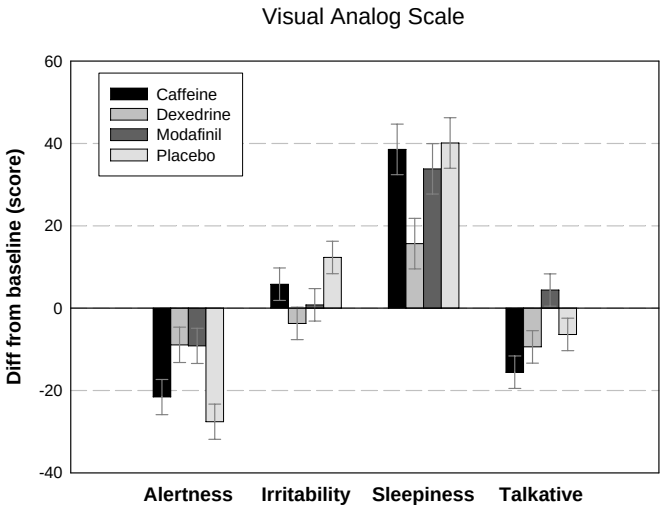

Figure 9. Significant drug main effects on four subscales of the VAS.

Significant session main effects were seen for (Al)ertness ($F(11, 308) = 7.867$, $p<0.000$), (E)nergy ($F(11, 308) = 12.390$, $p<0.000$), (C)onfidence ($F(11, 308) = 3.608$, $p<0.000$), (J)itteriness ($F(11, 308) = 2.483$, $p<0.0299$), and (S)leepiness scales ($F(11, 308) = 24.596$, $p<0.000$) of the VAS. Only the two-way interaction between session and drug on the sleep subscale proved significant. A post hoc comparison revealed that, in general, participants in the dextroamphetamine group reported significantly less sleepiness than the other groups (7 out of 12 sessions). The other groups were not significantly different in this respect except on sessions 1 and 3 (early and mid-morning of the first day) where the modafinil group reported significantly less sleepiness than the placebo group. In the late evening of both drug days (approximately 1800 hrs –2400 hrs) none of the groups differed significantly in their reported sleepiness (figures 10-11).

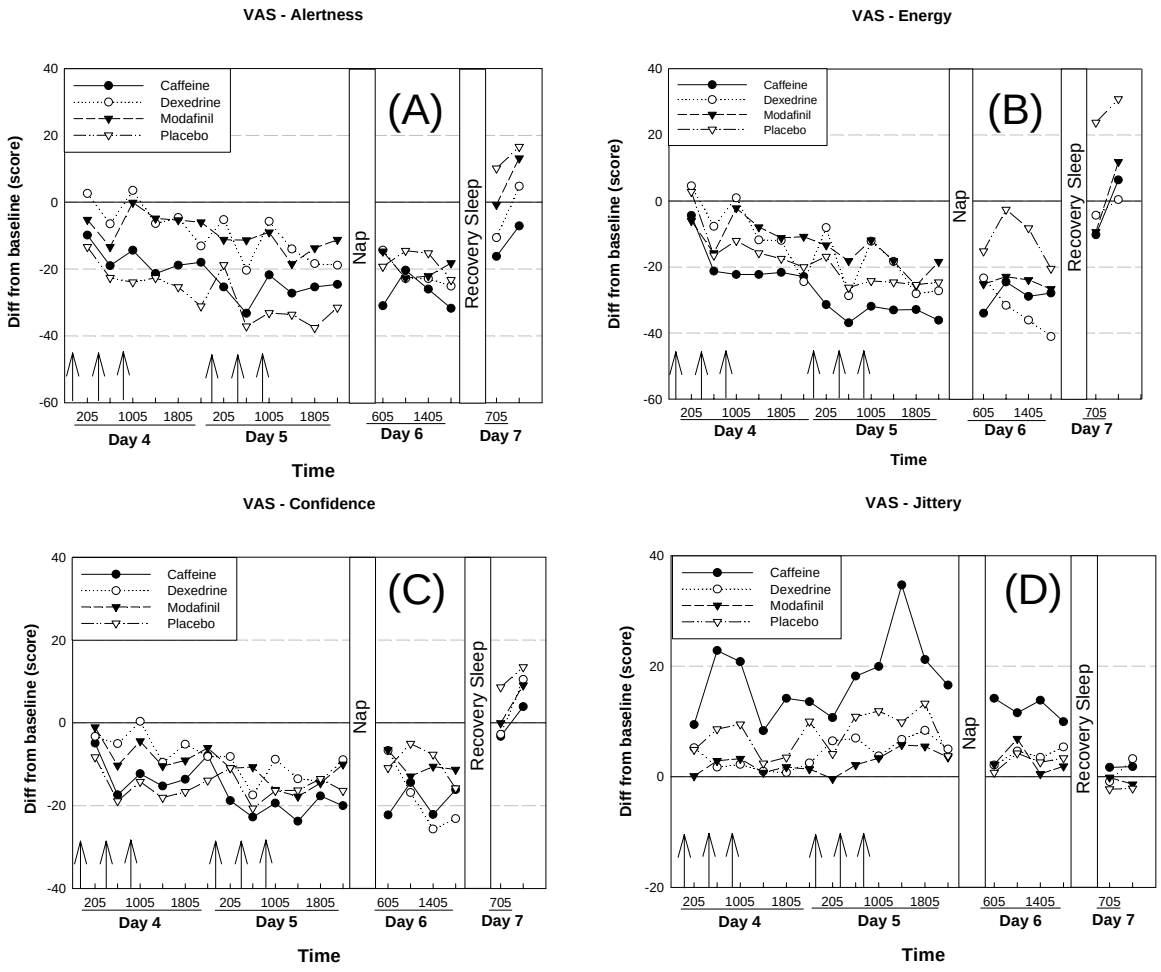

Figure 10. VAS data for four subscales across all test sessions: (A) Alertness, (B) Energy, (C) Confidence, and (D) Jittery.

The napping/sleep effects analysis showed a significant main effect for drug only on the talkativeness scale ($F(3, 28) = 3.501$, $p<0.028$). A Tukey HSD post hoc analysis showed that this difference was due to differences between the dextroamphetamine and placebo groups; placebo group being more talkative during this period that the dextroamphetamine group ($p<.05$). All scales except anxiousness showed significant main effects for session; Al ($F(6, 168) = 19.418$, $p<0.000$), E ($F(6, 168) = 30.650$, $p<0.000$), C ($F(6, 168) = 18.710$, $p<0.000$), J ($F(6, 168) = 3.946$, $p<0.006$), S ($F(6, 168) = 60.305$, $p<0.000$), I ($F(6, 168) = 2.909$, $p<0.017$), and T ($F(6, 168) = 9.726$, $p<0.000$). The interaction between drug and session show significance only on the talkativeness scale ($F(18, 168) = 1.952$, $p<0.015$). The post hoc analyses indicated that generally the placebo group was more talkative than the dextroamphetamine and caffeine groups, and that all groups felt significantly more talkative during the last testing session just prior to release (figure 11D).

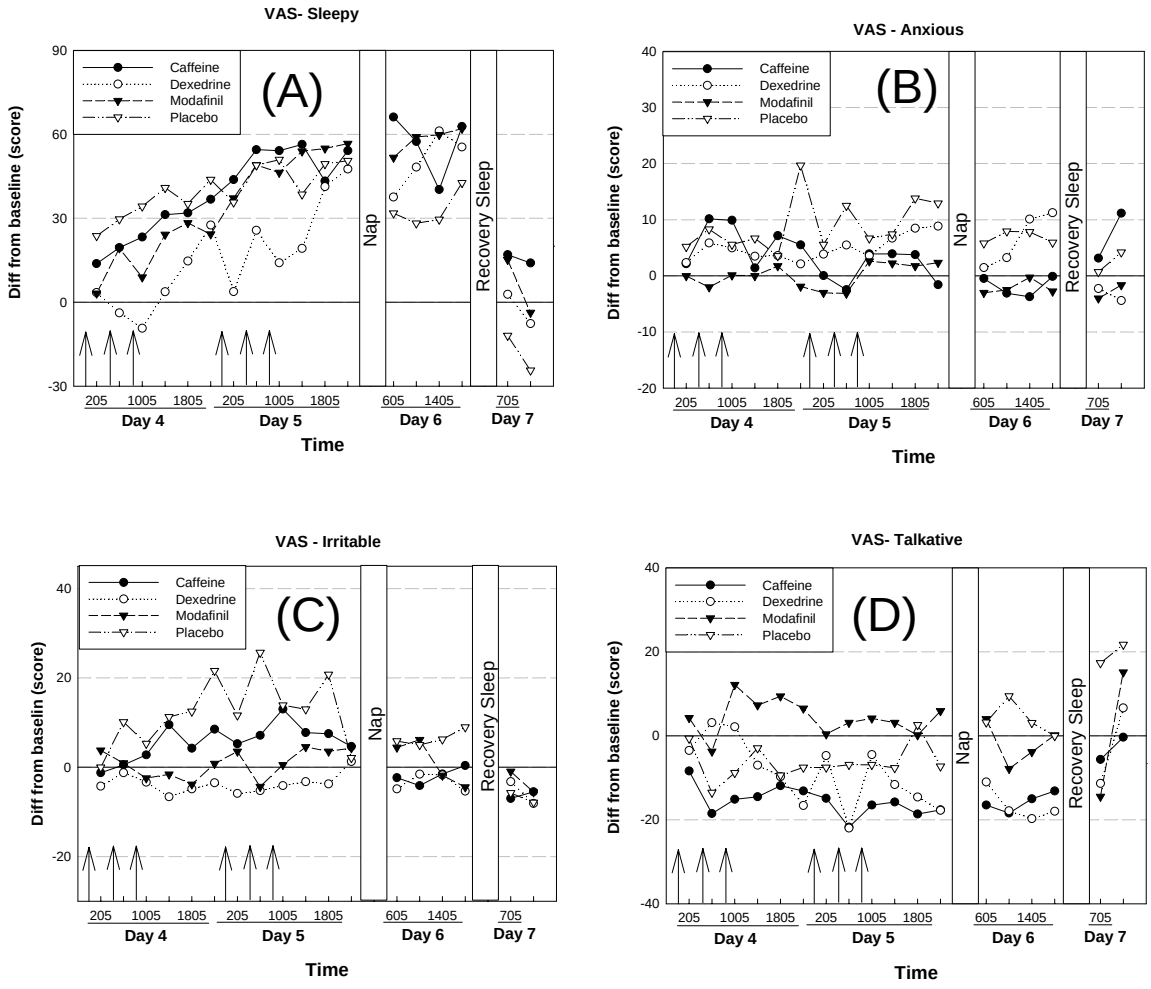

Figure 11. VAS data for four subscales across all test sessions: (A) Sleepiness, (B) Anxious, (C) Irritable, and (D) Talkative.

Simulator Sickness Questionnaire (SSQ)

SSQ were given after each simulator flight. Participants' responses on the SSQ questions loaded onto factors indicating symptoms of (N)ausea, (V) visuomotor/eye-strain, (D)isorientation, and (T)otal symptom severity. These data were subjected to an analysis of variance and revealed significant main effects for drug on all scales except disorientation (Figure 12), N ($F(3, 28) = 3.334$, $p<0.034$), V ($F(3, 28) = 3.951$, $p<0.018$), T ($F(3, 28) = 3.606$, $p<0.026$), and all sessions, N ($F(11, 308) = 2.521$, $p<0.024$), V ($F(11, 308) = 13.306$, $p<0.000$), D ($F(11, 308) = 4.758$, $p<0.000$), T ($F(11, 308) = 8.989$, $p<0.000$). The Tukey HSD analysis on the drug main effect indicated that generally the placebo and caffeine groups reported higher symptoms than the modafinil and dextroamphetamine groups, with only the differences between

the placebo group and dextroamphetamine group achieving significance ($p<.05$). Post hoc analysis of the session main effect indicated that across all scales of the SSQ, generally as the period of sleep deprivation lengthened, self-reported symptoms associated with simulator sickness increased. No session × drug interaction effects were significant.

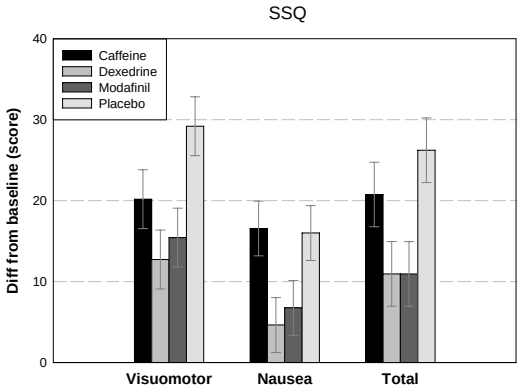

Figure 12. SSQ drug main effects.

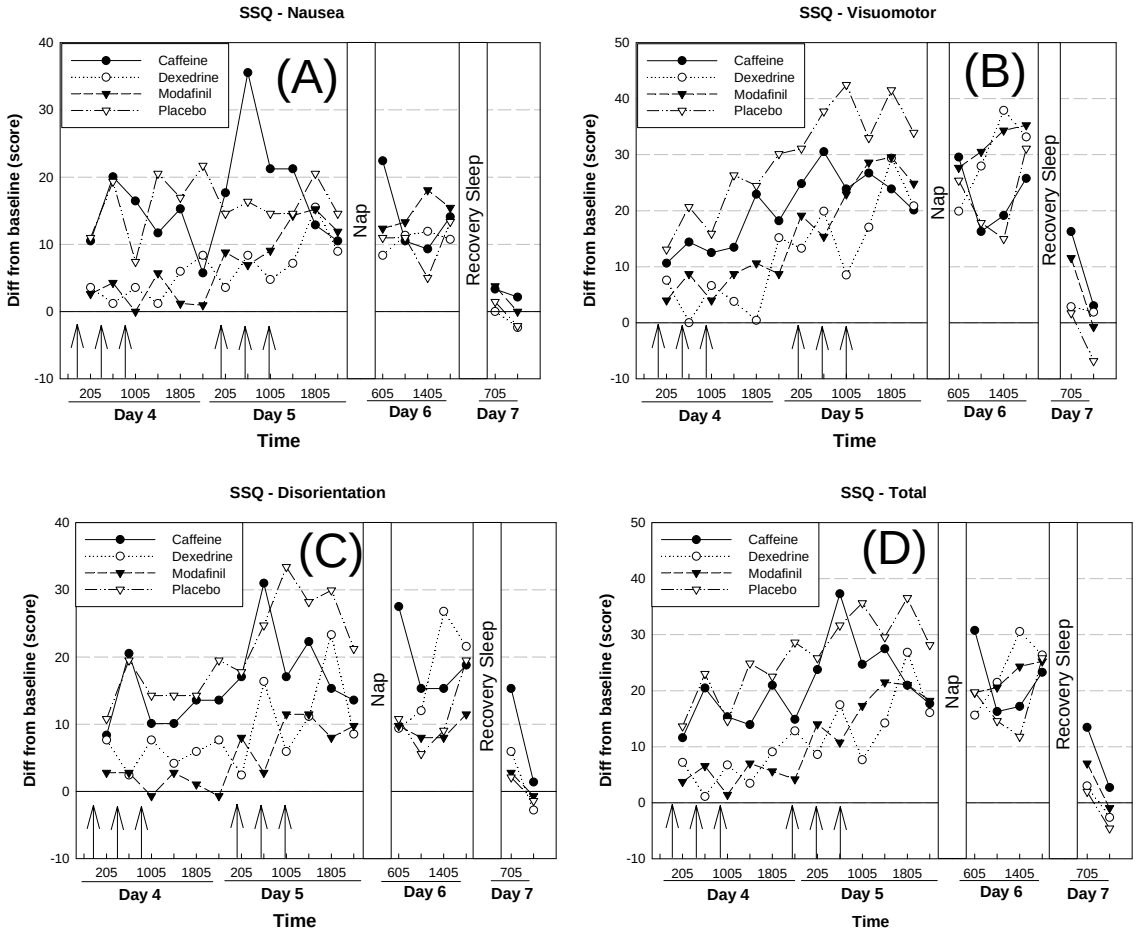

Figure 13. Simulator Sickness Questionnaire (SSQ) data for the four subscales across all test sessions: (A) Nausea, (B) Visuomotor, (C) Disorientation, and (D) Total.

The analysis examining the effects of napping and sleep on simulator symptoms did not indicate any main effects for drug, however, all subscales indicate significant main effects of session, N ($F(6, 168) = 9.247$, $p<0.000$), V ($F(6, 168) = 21.814$, $p<0.000$), D ($F(6, 168) = 7.670$, $p<0.000$), T ($F(6, 168) = 17.608$, $p<0.000$). Only the visuomotor subscale showed a significant session × drug interaction, V ($F(18, 168) = 1.705$, $p<0.045$). Post hoc analysis revealed this was due to significantly higher reports of visuomotor-related symptoms during the afternoon of day 6 by the dextroamphetamine group as compared to placebo, and by the placebo group's lower reports of these symptoms after the final flight as compared to the caffeine group (figure 13).

Symptom Checklists (SC)

Symptom checklists were given at 0410 and 0810 on both drug days (days 4 & 5). Analyses of the symptom checklist data showed drug main effects for the variables nausea ($F(3, 28) = 7.030$, $p<0.001$) (figure 14A); jitteriness ($F(3, 28) = 3.658$, $p<0.024$) (figure 14A); and nervousness ($F(3, 28) = 5.281$, $p<0.005$) (figure 14C). Post hoc analyses showed that these effects generally were produced by higher scores in the caffeine group than all other groups on all three of these symptoms ($p<.05$). Group differences for all other reported symptoms were non-significant.

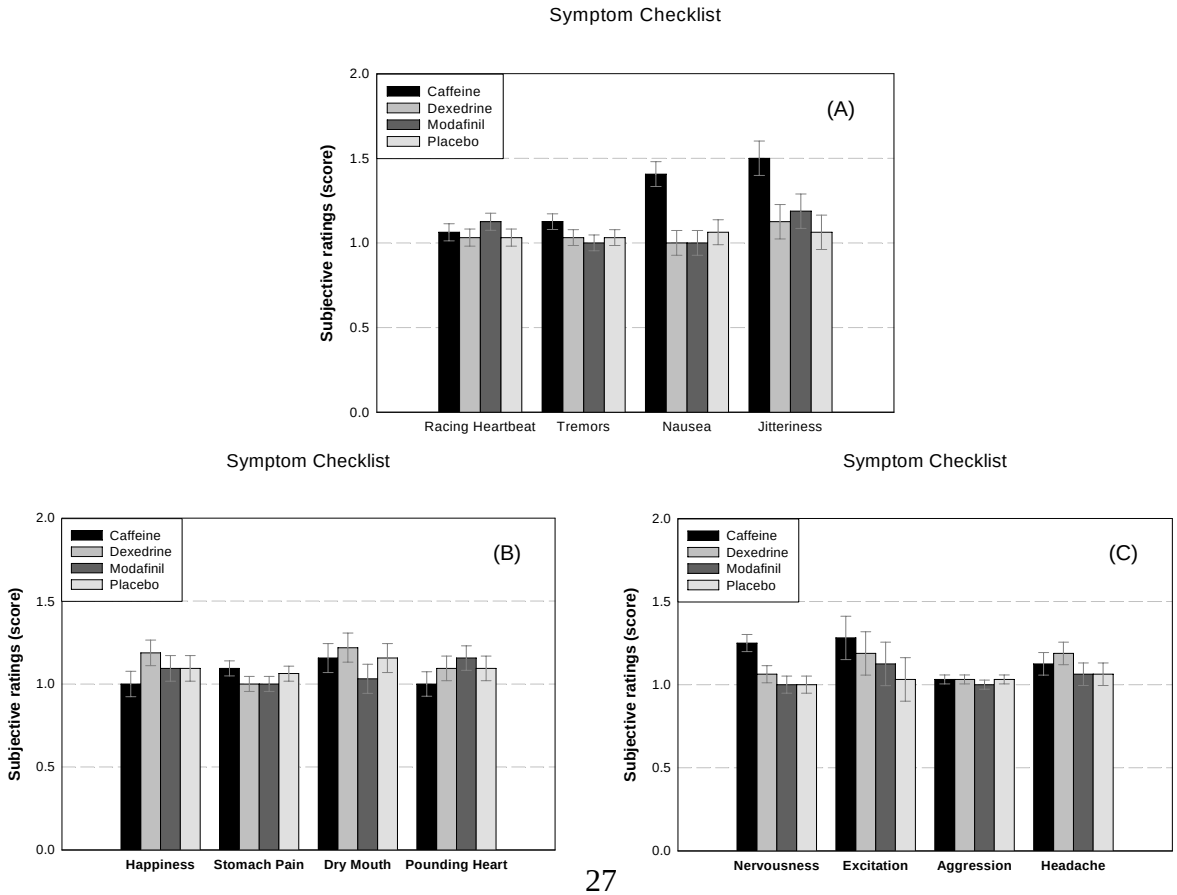

Figure 14. Symptom Checklist drug effects. Significant (p<0.05) for Nausea and Jitteriness (A), and Nervousness (C).

Evaluation of Risks (EVAR)

The EVAR measured the propensity to engage in or avoid risky behavior and situations where participants marked a point along a 100mm bipolar visual analogue scale to indicate their preference for various types of risky activities. The EVAR was administered once at 2130 on day 3 to determine baseline and again at 2130 during the both following sleep deprivation days (day 4 and day 5). Data are expressed as change from baseline and were subjected to an analysis of variance that indicated there were no significant differences among drug groups for any of the EVAR's three derived measures.

Performance Tests

Psychomotor Vigilance Task (PVT)

Analyses of the sleep deprivation data from the PVT showed no significant main effects for drug group on reaction time. Significant session reaction times were present (F(5,140) = 7.395, p<0.003). The post hoc test for session showed a general increase in mean reaction time as the length of sleep deprivation increased. This effect was most evident within the placebo and modafinil groups, but the session × drug interaction was not significant.

The sleep/nap data analysis indicated similar effects; session (F(3,28) = 5.405, p<0.004). The post hoc analysis on these sleep related data showed that only the modafinil group benefited from the nap, and that all groups except modafinil saw significant improvement in reaction time following recovery sleep as compared to pre-recovery sleep (figure 15).

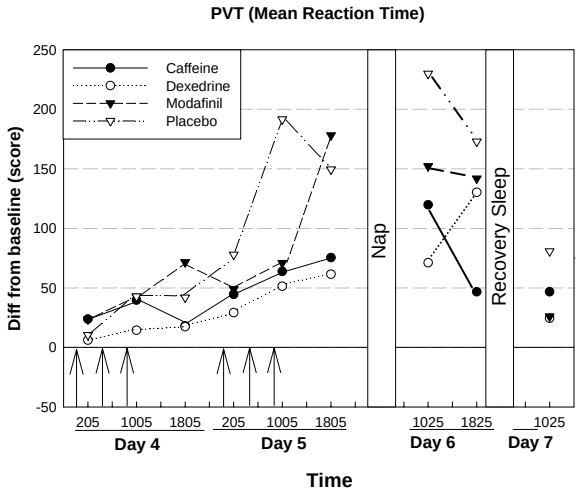

Figure 15. Baseline corrected mean reaction time in milliseconds on the PVT across all sessions.

CANTAB

The CANTAB used touch-screen technology to deliver rapid, non-invasive, language-independent cognitive tests. It is well validated and suitable for repeated measures testing. The following subtests were chosen based upon a review of the open literature papers that have used CANTAB to assess the effects of stimulants. Each test generated numerous derivative measures, however, only the primary measures or those most salient to the current study are discussed here.

Reaction Time (RTI). This component of the CANTAB tested simple (single) and multiple choice reaction times. The participant touched the screen when a yellow dot was displayed. For the multiple choice reaction time task, the dot was shown in one of five locations. Response measures were Simple Reaction Time (SRT), Simple Movement Time (SMT), Five-choice Reaction Time (FRT), and Five-choice Movement Time (FMT). An analysis of variance on these data during the sleep deprivation period revealed no main effect of drug on any of the measures. Conversely, all session main effects were significant; SRT ($F(3, 84) = 6.584$, $p<0.001$), SMT ($F(3, 28) = 4.441$, $p<0.006$), FRT ($F(3, 84) = 9.140$, $p<0.000$), and FMT ($F(3, 84) = 3.366$, $p<0.022$). The Tukey post hoc analysis indicated these session effects were due to increased times in sessions 3 and 4 compared to session 1 and 2. No interaction effects between session and drug were found (figure 16).

Analysis of the effects of napping and sleep on RTI performance yielded similar results. Drug main effects were not significant; all session main effects were significant; SRT ($F(3, 84) = 3.033$, $p<0.035$), SMT ($F(3, 28) = 6.537$, $p<0.002$), FRT ($F(3, 84) = 7.862$, $p<0.000$), and FMT ($F(3, 84) = 7.207$, $p<0.000$). The Tukey post hoc analysis indicated these session effects generally were due to increased reaction and movement times upon awakening from the nap. Again, no interaction effects between session and drug were found.

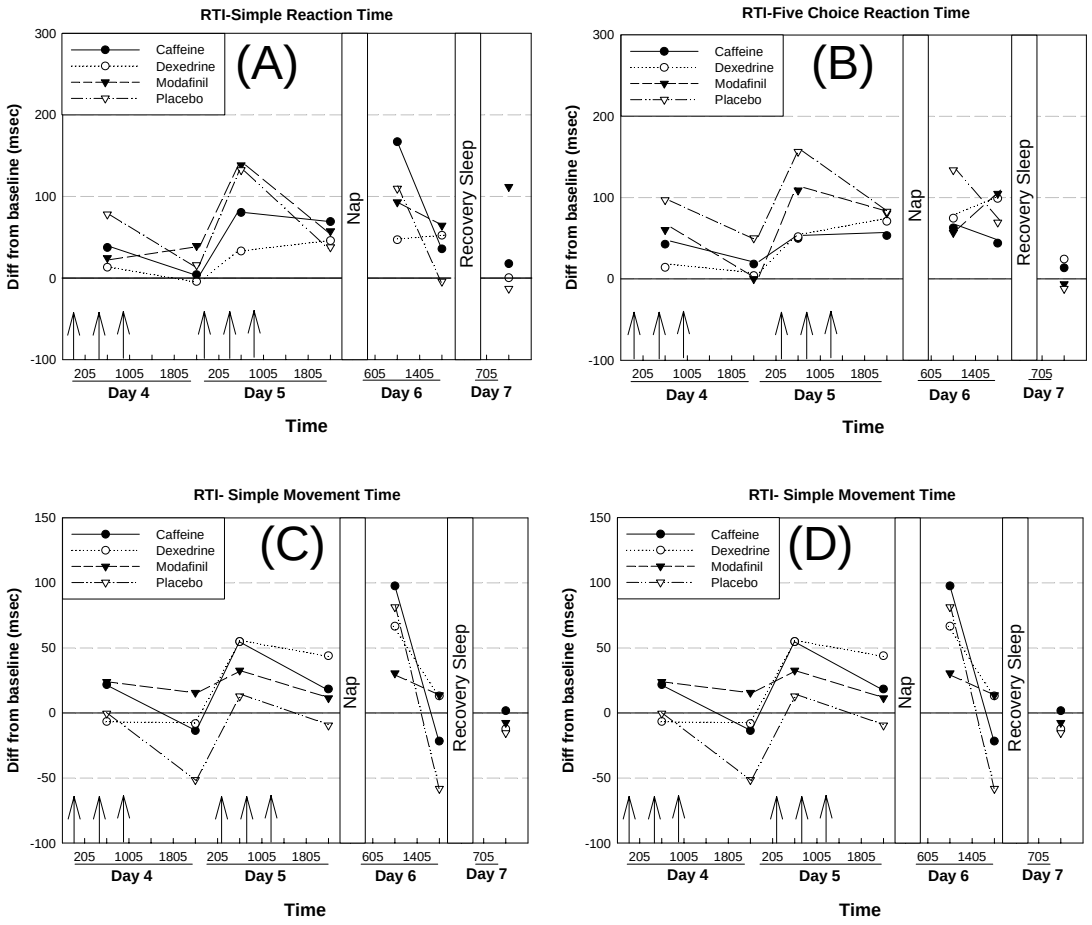

Figure 16. RTI Simple (A) and Five Choice (B) reaction time, and Simple (C) and Five Choice (D) movement time across all sessions by drug group.

Matching to Sample Visual Search (MTS). MTS is a speed/accuracy trade-off task that tested the participant's ability to match visual samples and measured their reaction and movement time. Only the primary measures for latency and percent correct are reported here (figure 17). These data demonstrated no main effect for drug on either measure during sleep deprivation. Session main effects were significant for latency ($F(3, 84) = 4.967$, $p<0.006$). The session post hoc analysis for latency showed that on day 5 (sessions 3 & 4) participants were taking significantly longer to respond than on day 4 (sessions 1 & 2). Session × drug interactions were non significant even with the spike in latency for placebo at the end of day five. The sleep/nap analysis yielded no significant main effects for drug. Session main effects again were significant for latency ($F(2, 56) = 10.240$, $p<0.000$). Session × drug interactions also were significant for latency ($F(6, 56) = 3.451$, $p<0.006$). The post hoc analyses indicated that responses were faster after the nap/sleep periods as compared to the pre nap latency, and that the placebo group benefited the most from the nap/sleep.

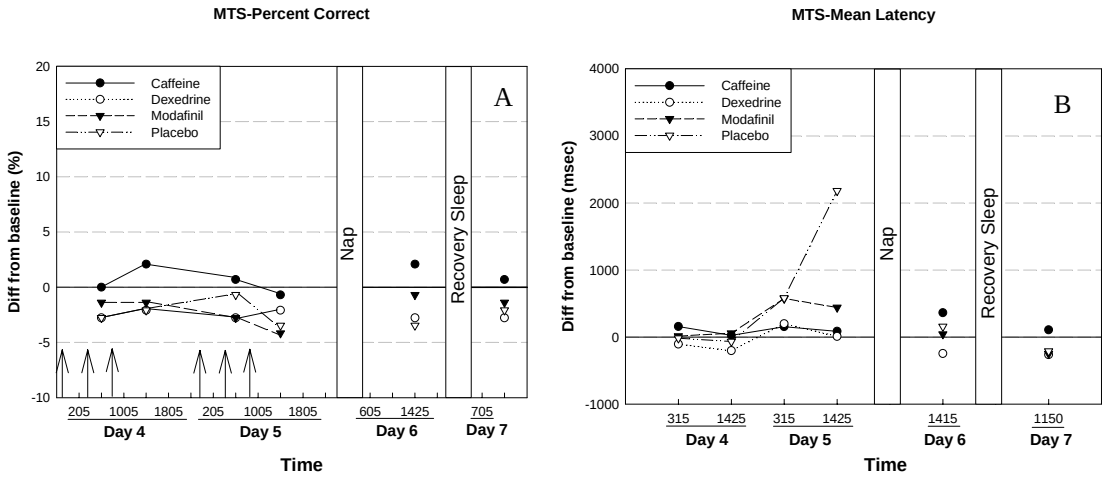

Figure 17. Mean percent correct (A) and mean latency (B) in milliseconds on MTS across all sessions.

Rapid Visual Information Processing (RVP). The RVP is a test of visual sustained attention with a small working memory component. Response measures follow a signal detection paradigm; hits (H), misses (M), false alarms (FA), correct rejections (R), and response latency (L) (figure 18A-E). The derived measure A-prime (A'), the sensitivity to the target regardless of response tendency, was also used[1] (figure 18F). The analysis of variance on the sleep deprivation data resulted in significant differences among drug groups for hits, misses, correct rejections, and A'; H ($F(3, 28) = 7.041$, $p<0.001$, M ($F(3, 28) = 6.724$, $p<0.001$), R ($F(3, 28) = 5.169$, $p<0.006$), and A' ($F(3, 28) = 10.655$, $p<0.000$). In all cases post hoc analyses showed this was due to significantly worse performance by the placebo group than all the other drug groups. The session main effects were significant for all measures except latency; H ($F(3, 84) = 7.921$, $p<0.000$), M ($F(3, 84) = 7.921$, $p<0.000$), FA ($F(3, 84) = 4.699$, $p<0.017$), R ($F(3, 84) = 7.380$, $p<0.000$), and A' ($F(3, 84) = 10.766$, $p<0.000$). Post hoc analyses indicated this was due to sessions 1 and 2 being significantly different from sessions 3 and 4. None of the session × drug effects were significant.

The nap/sleep analysis showed a significant drug effect only for hits ($F(3, 28) = 3.003$, $p<0.047$), and A' ($F(3, 28) = 3.228$, $p<0.037$). In this case, the significant differences were only between the caffeine and placebo groups. All session main effects were significant; H ($F(2, 56) = 13.809$, $p<0.000$), M ($F(2, 56) = 13.809$, $p<0.000$), FA ($F(2, 56) = 3.432$, $p<0.039$), R ($F(2, 56) = 12.504$, $p<0.000$), L ($F(2, 56) = 7.045$, $p<0.002$), and A' ($F(2, 56) = 26.606$, $p<0.000$). Post hoc analyses indicated this generally was due to significantly different scores in session 3 (post sleep) as compared to sessions 1 (pre nap) and 2 (post nap). The A' post hoc analyses showed no benefit from the nap, but significant improvement after restorative sleep. In addition, the placebo group was worse overall than the modafinil and caffeine groups, but was not significantly different from the dextroamphetamine group. Again, none of the session × drug effects were significant.

[1] A' has been shown to be sensitive to pharmacological manipulation by cholinergic agonists such as nicotine (Sahakian et al., 1989).

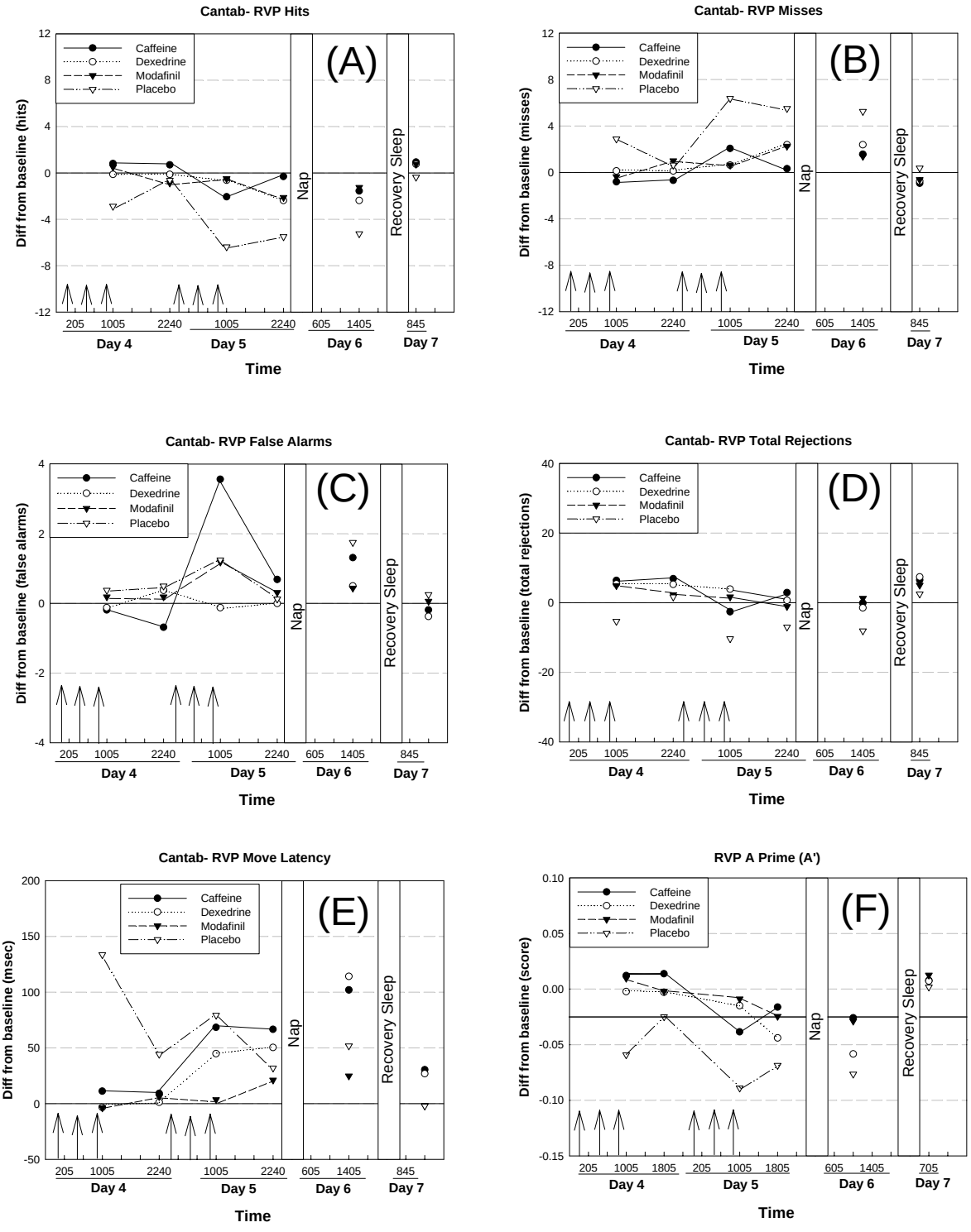

Figure 18. Rapid Visual Information Processing (RVP) data for the six subscales across all test sessions: (A) Hits, (B) Misses, (C) False Alarms, (D) Rejections, (E) Latency, and (F) A prime.

Stockings of Cambridge (SOC). This is a test of spatial reasoning based upon the 'Tower of London' test. The subject was shown two displays containing three colored balls. The subject used the balls in the lower display to copy the pattern shown in the upper one. The fundamental response measure, number of problems solved in minimum moves (PS), was a succinct expression of overall planning accuracy that recorded the occasions upon which the subject completed a test problem in the fewest possible number of moves (figure 19).

Analysis of variance on the sleep deprivation data revealed no significant main effect among drug groups. There was a significant main effect for session, ($F(3, 84) = 3.898$, $p<0.012$), but no drug × session interaction. Post hoc analyses by session revealed performance during sessions 1 and 3 during the drug test days was significantly better than performance during session 4 just before the nap.

The nap/sleep analysis again showed no significant main effect for drug, a significant main effect for session ($F(2, 56) = 6.494$, $p<0.003$), and no significant drug × session interaction. This post hoc analysis showed that significant differences were due to the pre nap session being higher than the post nap session. The recovery sleep period did not significantly affect PS performance difference from baseline scores.

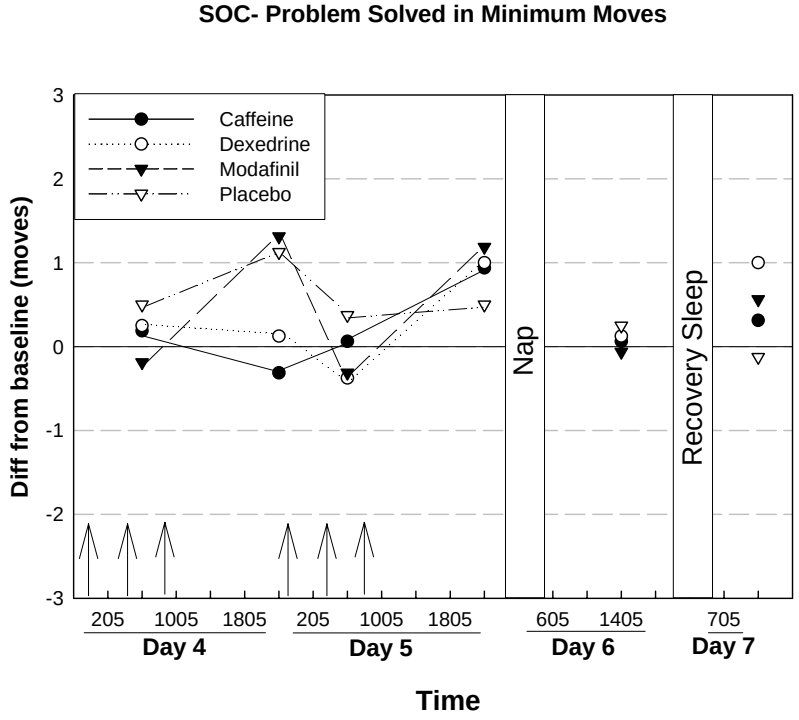

Figure 19. Baseline corrected scores for Stocking of Cambridge task indicating number of problems solved in minimum number of moves.

WOMBAT

The WOMBAT procedure consists of generalized flight-based tasks that require situational awareness and crew resource management. Performance is measured in two conditions- the individual and duo settings. The individual mode is comprised of three subtasks: three-(D) figure rotation, (Q)uadrant location and digit (C)ancellation. These tasks are performed by the participant as an autonomous individual, although the other participant is present during the performance of these tasks. These data are presented in figure 20. In contrast, the duo-mode, uses three of the same basic subtasks – D, Q, and C – but is performed simultaneously by both participants. (T)racking was a fourth subtask present only in the duo mode. In this mode, communication, resource management, and crew coordination were paramount. Scores reflected the pair of participants' ability to strive toward mutual goals, keeping lines of communication open and avoiding conflict over control/decision making. Overall duo WOMBAT data are presented in figure 22.

The WOMBAT data were first analyzed over the two-day sleep deprivation period, in order to elucidate any differential effects of drug preparation over time. All seven subtasks (three individual and four duo) were analyzed together in a mixed model multivariate analysis of variance (MANOVA). The WOMBAT data were then analyzed with respect to the effects of the two-hour nap following the sleep deprivation period.

Individual WOMBAT. For the three individual WOMBAT subtasks, there were no significant main effects of drug condition during sleep deprivation. Likewise, there were no significant session main effects for any subtask. Interaction effects between drug condition and session were demonstrated only in the digit cancellation task ($F(15,105) = 3.181$, $p<0.001$). Post hoc tests on digit cancellation showed that drug group scores differed at the second, fourth and fifth sessions ($p<0.05$). During session two, dextroamphetamine group scores were higher than those in the modafinil and placebo group. Also at that time, the caffeine group scores were higher than the placebo group scores. In session 4, the dextroamphetamine group's scores were superior to both the caffeine and the modafinil group scores. Then at session five, the scores from the dextroamphetamine group were higher than both the caffeine group and placebo group scores.

For the post nap analysis, the digit cancellation task produced the only main effect for drug ($F(3,26) = 3.138$, $p<0.042$) (figure 21). Follow up contrasts (Tukey HSD) failed to reveal any specific pattern of significant differences among drug conditions. Only quadrant location demonstrated a significant session main effect ($F(2,52) = 4.235$, $p<0.020$).

Interactions of drug condition and session effects were demonstrated in two of the individual subtasks; D ($F(6,42) = 2.413$, $p<0.047$), Q ($F(6,42) = 2.960$, $p<0.015$)). Post hoc comparisons revealed differences between pre and post nap performance; an effect that varied with drug group membership ($p<0.05$). For three-dimensional rotation, the nap generally did not improve performance and in fact, the dextroamphetamine group scored significantly lower during the first post nap session, and the caffeine group's pre nap scores were lower than the second post nap scores. No differences were revealed between pre and post nap performance in the modafinil

group or in the placebo group for this variable. For quadrant location, scores in the caffeine group improved by the second post nap session. However, in the placebo group, pre nap performance was superior to that of the first post nap session. No intersession differences were seen in either the dextroamphetamine or the modafinil group for this variable.

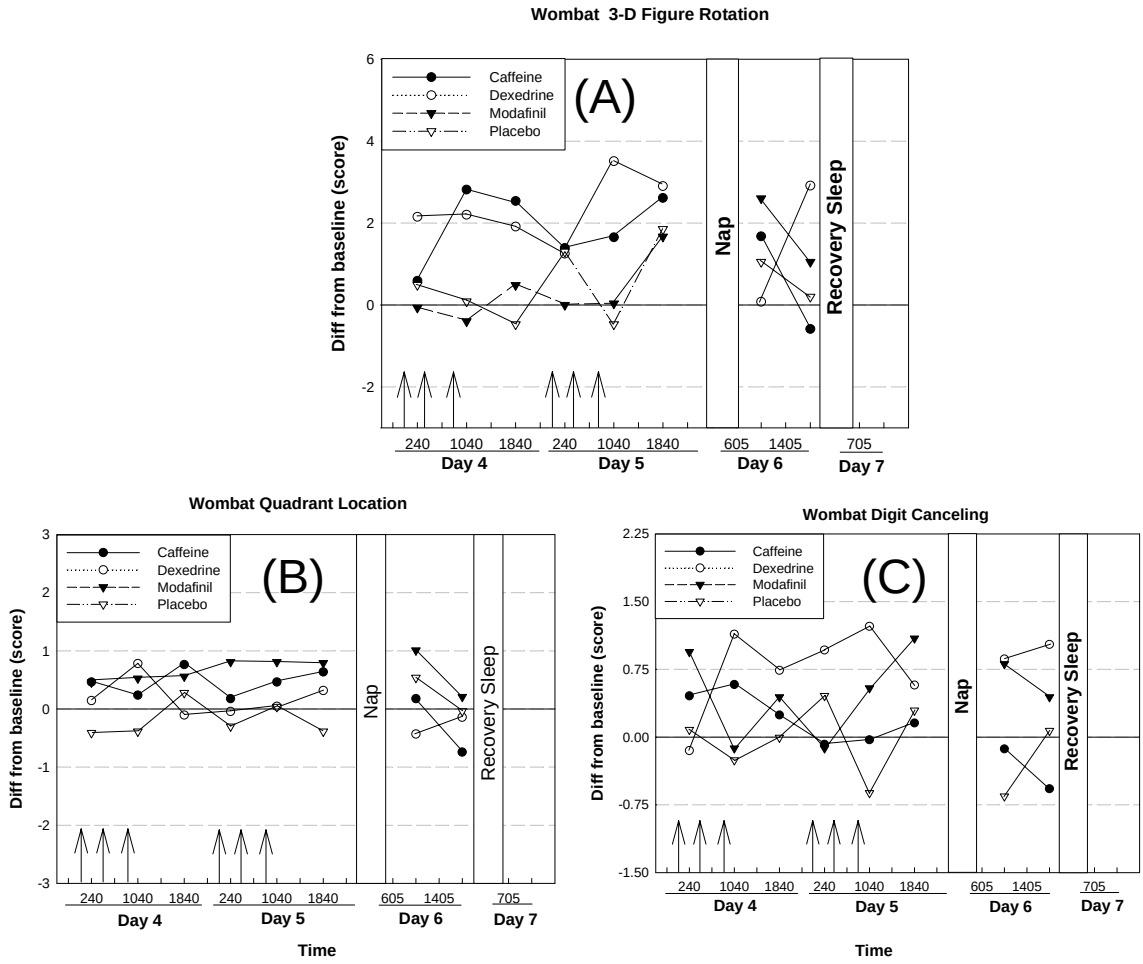

Figure 20. Performance on the individual tasks of the WOMBAT shown by drug group across all test sessions.

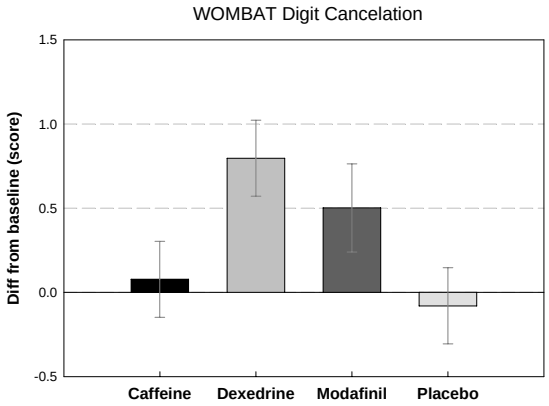

Figure 21. Drug main effect on WOMBAT digit cancellation, during the nap/sleep period (p< 0.043) (higher score is better).

DUO WOMBAT. For the four duo WOMBAT subtasks, there were no significant main effects for drug condition during sleep deprivation, nor were there any session main effects. In terms of drug × session interaction, only digit cancellation ($F(15,105) = 3.120$, $p<0.001$), and tracking reached significance ($F(15,105) = 2.717$, $p<0.001$). Post hoc tests revealed differences for the digit cancellation task only at session five ($p<0.05$). At that time, scores in the dextroamphetamine group were slightly, but significantly, lower than the caffeine group. There were no other pairwise differences demonstrated for the digit cancellation task. For the tracking subtask, scores differed among drug conditions only during test sessions one, three and six ($p<0.05$). During session one, the dextroamphetamine group scored lower than the other groups. During session three, the dextroamphetamine and the placebo group each scored lower than the modafinil group, but did not differ from one another. At session six, scores in the modafinil group significantly exceeded scores in the dextroamphetamine group.

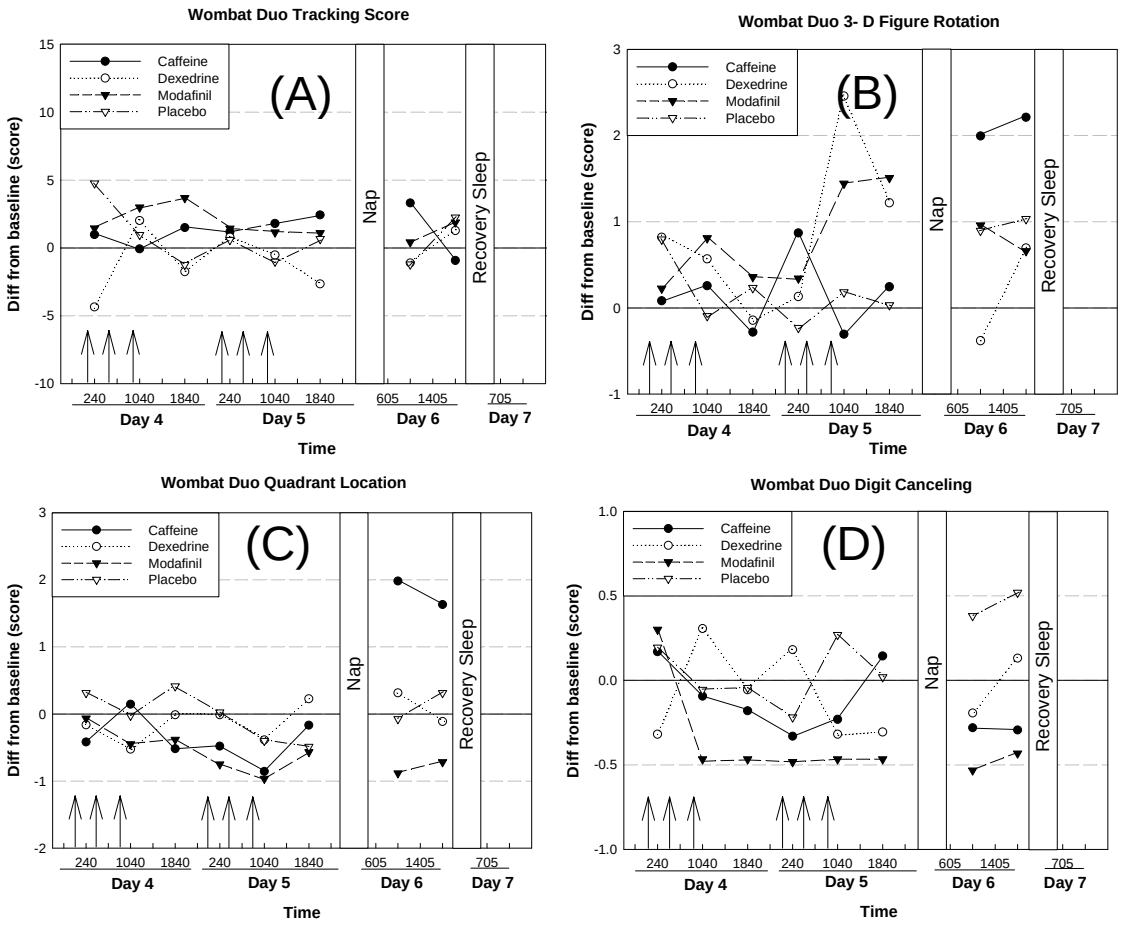

Figure 22. Performance on the Duo (Dual-participant) tasks of the WOMBAT, shown by drug group across all test sessions.

For the post nap analysis, no significant main effects for drug condition were found. Likewise, there were no significant session main effects for these tasks. However, an interaction between drug condition and session was revealed on three subtasks; tracking ($F(6,42) = 2.683$, $p<0.032$), quadrant location ($F(6,42) = 2.700$, $p<0.023$), and digit cancellation ($F(6,7) = 5.856$, $p<0.001$). Post hoc comparisons revealed differences between pre and post nap performance that varied depending upon drug condition ($p<0.05$). For the tracking task, the first post nap session generally was no different from pre nap, but scores improved by the second post nap session. The exception to this was the caffeine group whose performance decreased during the second post nap session. For quadrant location, in the caffeine group, pre nap performance was poorer than scores from both of the post nap sessions. No intersession differences were seen in the dextroamphetamine or the modafinil groups. In the placebo group, pre nap performance was again poorer than that of the second post nap session. In the digit cancellation subtask, for the caffeine group, pre nap performance was poorer than that of both post nap sessions. The reverse held true in the dextroamphetamine and placebo groups, where performance degraded after the nap. The modafinil group, once again, did not yield any intersession differences.

Flight Performance

The flight data consisted of seven standard maneuvers (H)over, straight and level VMC flight (SLv), constant radius turn VMC (Tv), (C)limb, constant radius turn IMC (Ti), straight and level flight while under IMC (SLi), and an (ILS) approach. Each score was a composite taken from the various components required to perform the maneuver. Some maneuvers were performed under visual meteorological conditions (VMC), under instrument meteorological conditions (IMC), and/or using the instrument landing system (ILS) The magnitude of the score (percent of 100) represented the degree to which the subject maintained the required standard. A subject's change from baseline performance was used to adjust for any naturally occurring differences due to ability or experience. The objective performance data taken from the NUH-60 simulator are presented in figure 23.

These data yielded a significant main effect during sleep deprivation among the drug groups for hover ($F(3, 28) = 4.476$, $p<0.011$), and climb ($F(3, 28) = 3.977$, $p<0.018$). Post hoc analysis revealed this resulted from the modafinil group's superior performance as compared to the dextroamphetamine group on the hover maneuver, and the dextroamphetamine group's superior performance than placebo in the climb maneuver ($p<0.05$) (figure 23). Neither session effects, nor drug × session interactions were significant.

Analysis of the nap/sleep period flights revealed no significant main effects among drug groups, no main effects among sessions, nor any drug × session interactions.

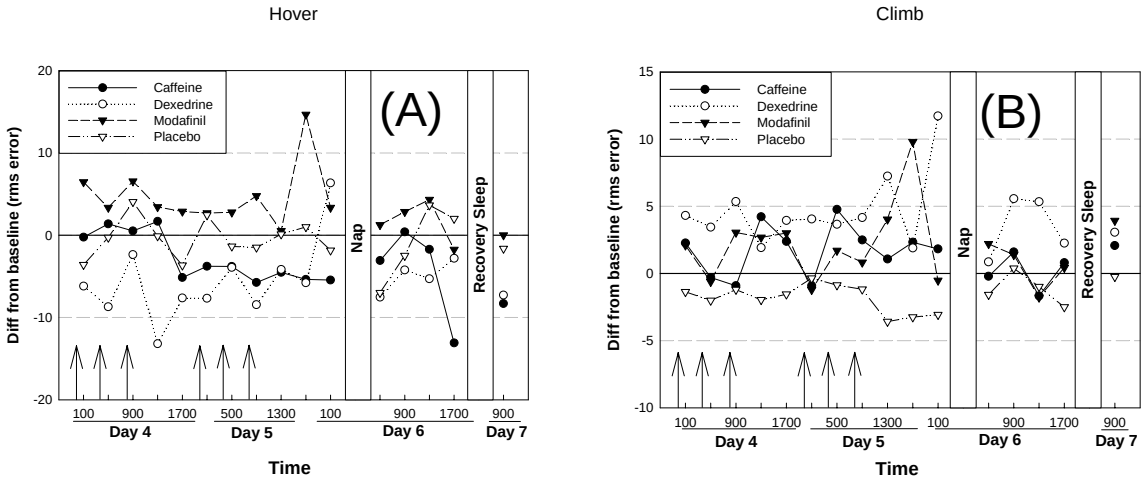

Figure 23. Flight performance in the NUH-60 flight simulator for (A) hover, and (B) climb. Data plotted for each drug group across all sessions.

Retrospective comparisons

We have taken this opportunity to compare briefly some of the data from earlier studies using 3 × 10 mg doses of dextroamphetamine (Caldwell, 1999a, 1999b) or 3 × 200 mg doses of modafinil (2000b) with the data collected in the present study. Portions of the methodology from these studies (certain flight maneuvers, the Visual Analog Scale and the Profile of Moods State) were identical to previous studies allowing direct comparisons that can help begin to determine the optimal effective dose necessary to sustain performance in aviators during extended operations.

Flight Performance

Although several clear patterns emerge, few significant differences exist between data from the earlier dextroamphetamine studies and the current data. There was a significant main effect for dose on hover performance ($F(1, 12) = 8.888$, $p<0.011$). Post hoc tests indicated superior simulator hover performance in the high dosage group (figure 24). In addition, there were no significant session effects on any of the maneuvers, or any dose × session interactions.

The modafinil data indicated there were no significant differences between doses on any of the maneuvers. Likewise, there were no significant session effects on any of the maneuvers, or any dose × session interactions.

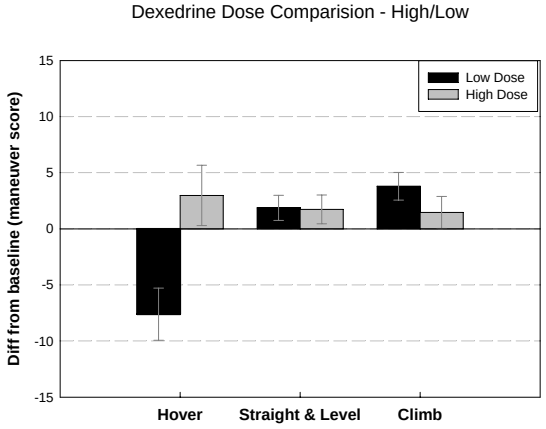

Figure 24. Comparison between low (3 x 5 mg) and high (3 x 10 mg) doses of dextroamphetamine on comparable flight performance maneuvers.

Profile of Mood States

POMS data for the two studies were compared across six independent subscales and revealed no main effect for dose of dextroamphetamine on any of the scales. There were significant session main effects for vigor, and fatigue, and confusion; V ($F(5, 120) = 8.322$, $p< 0.000$), F ($F(5, 120) = 5.948$, $p< 0.001$) , and C ($F(5, 120) = 2.830$, $p< 0.044$); but no interactions between dose and session achieved significance.

POMS data for the two studies also were compared across the six subscales and revealed only a main effect for dose of modafinil on the tension scale; the higher dose reported more tension; ($F(1, 12) = 7.223$, $p< 0.20$). Significant main effects for session were seen on the tension, vigor, fatigue, and confusion scales; T ($F(5, 60) = 3.203$, $p< 0.014$) , V ($F(5, 60) = 6.091$, $p< 0.001$), F ($F(5, 60) = 7.377$, $p< 0.000$), and C ($F(5, 60) = 4.182$, < 0.008); in addition, interactions between dose and session achieved significance for fatigue ($F(5, 60) = 2.788$, $p< 0.040$). Post hoc analyses for the fatigue interaction revealed that the greatest differences between doses occurred during the last session, but the pairwise difference was not significant ($p<0.076$) (Figure 25).

Visual Analog Scale

The VAS was used in each study and analyses for comparable data showed a significant difference only for reports of irritability between the two doses of dextroamphetamine (figure 26) ($F(1, 12) = 5.095$, $p<0.043$). Post hoc analyses indicated that these differences were due to significantly lower reports of irritability in the low dose group. Significant session main effects were seen for measures of alertness, energy, confidence, and sleepiness, and talkativeness, Al ($F(5, 60) = 6.958$, $p<0.001$), E ($F(5, 60) = 7.147$, $p<0.000$), C ($F(5, 60) = 2.852$, $p<0.022$), S ($F(5, 60) = 5.975$, $p<0.002$), and T ($F(5, 60) = 7.638$, $p< 0.000$); but there were no significant session by dose interactions for any of the VAS scales.

An examination of the modafinil VAS data between the comparable studies showed no significant differences between the two doses on any of the VAS scales. Session main effects for modafinil were significant for energy ($F(5, 60) = 4.056$, $p<0.005$), and sleepiness ($F(5, 60) = 6.477$, $p<0.000$). Only the energy and talkativeness scales revealed significant session by dose interactions; E ($F(5, 60) = 3.483$, $p<0.011$), and T ($F(5, 60) = 2.723$, $p< 0.042$). Post hoc analyses on these data for talkativeness did not reveal pairwise significance; however, the energy data were significantly different between doses on the last session (Figure 26).

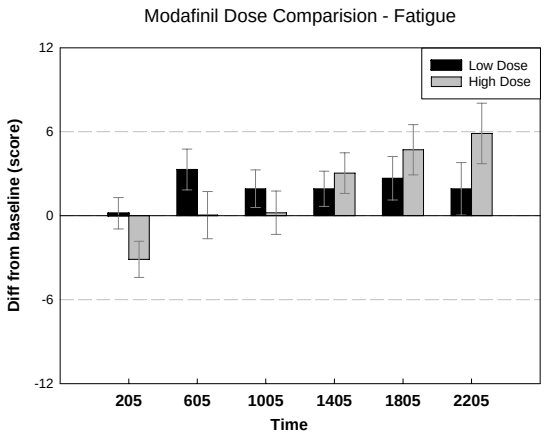

Figure 25. POMS data comparison between low dose (3 x 100mg) and high (3 x 200mg) modafinil studies showing dose by session effects for the fatigue scale (p<.05).

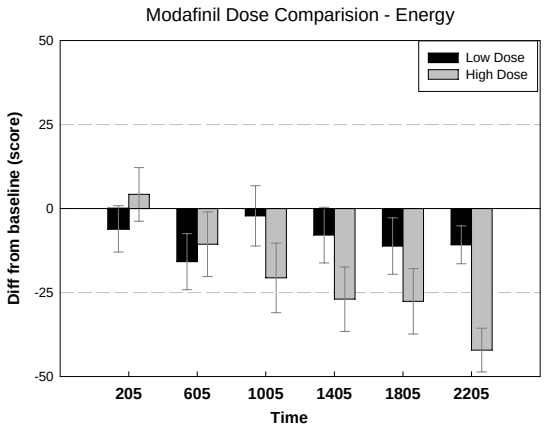

Figure 26. Comparison between low (3 x 100 mg) and high (3 x 200 mg) doses of modafinil by session on the Energy scales of the VAS (p<0.05).

Discussion

In this study, thirty-two helicopter pilots each completed twenty-two simulated UH-60 flights and a variety of other evaluations during 87 hours of sustained operations (68hr continuous plus an additional 17hr period after a 2 hour nap). The general findings from this investigation were that dextroamphetamine and modafinil similarly attenuated a number of the problems associated with sleep loss. While caffeine had some benefits in preventing performance decline typically seen with sleep deprivation, changes in performance in the caffeine group often mimicked those seen in the placebo group. The benefits of all three stimulants were most noticeable from approximately 0200 until 1000 when the fatigue from sleep deprivation was greatest. However, there were statistically significant differences on some measures in the afternoon as well, during the expected hemi-circadian low. The most consistent drug effects were observed on physiological measures (minimum and maximum pupil diameter and heart rate, figures 2 and 3B,

respectively) and self-reported mood (alertness, sleepiness, vigor, and fatigue) (figure 8), but a number of performance effects were seen as well (figures 20, 21, 22, and 23).

Vital signs and side effects

Both dextroamphetamine and modafinil significantly increased heart rate in these volunteers above the level seen in the placebo and caffeine groups. Similar increases in heart rate have been reported by other researchers and are listed as potential side effects in the PDR and product monographs (Eddy et al, 2004, Muller et al, 2004; Cephalon, 2004; PDR 2004). Unlike the other stimulant groups, the caffeine group actually exhibited an overall decrease in heart rate of about four beats per minute. While this result may seem surprising, it should be noted that the caffeine group reported increases in nausea, fatigue, tension, sleepiness, and decreases in vigor and alertness. Reports to staff members from several of the caffeine volunteers indicated that they preferred to sit quietly during breaks rather than engage in any of the activities available (darts, movies, cards, video games) because of the side effects. Few, if any, volunteers from the other groups complained about nausea or upset stomachs. Changes in pupil diameter were also found in both the dextroamphetamine and modafinil groups. Increases in minimum and maximum pupil size during the drug testing phase were highest in dextroamphetamine and modafinil groups. This finding is not unusual as pupil dilation (mydriasis) is commonly produced by stimulant administration (PDR, 2004). No differences in these ocular measures were noted between the caffeine and placebo groups. Whether these pupillary changes have psychophysical consequences, e.g. glare or contrast sensitivity, acuity and/or dark adaptation, may be an important question depending on mission requirements.

The most common side effect reported by participants in this study was nausea. Data from the SSQ showed that nausea rates in the caffeine and placebo groups nearly doubled, during the 68 hours of continuous wakefulness, those reported by the dextroamphetamine and modafinil groups (figure 13). The caffeine group also reported on the symptom checklist higher rates of nausea and jitteriness associated with drug administration. It should be noted that none of the modafinil-related side effects reported by Caldwell et al. (1999a; vertigo, dizziness, and nausea) were observed in the modafinil group in this study. This finding lends support for the use of the lower 3x100mg regimen compared to the 3x200mg doses employed by Caldwell et al. Several recent studies have suggested that symptoms such as nausea, vertigo and jitteriness seen with modafinil use may be dose dependent (Buguet et al., 2003; Eddy et al., 2005; Wesensten et al, 2002). Wesensten et al. (2002) found that 400mg of modafinil produced more frequent reports of nausea when given 41.5 hours post wake than did the 100mg or 200mg doses. The authors also reported one case of extreme jitteriness and shaking in the 400mg modafinil group. Additionally, several subjects in Wesensten's 600mg caffeine group reported nausea and two experienced vomiting.

Mood

Self-reported vigor, energy, alertness, talkativeness, and confidence decline was most apparent in the caffeine and placebo groups (figures 7 and 8). The decline in mood tended to happen at a faster rate over the beginning of the 68 hour period of sleep loss. However, by the last test session prior to the 2 hour nap, all four treatment groups reported similar declines in these mood ratings. Conversely, ratings of fatigue, jitteriness, and sleepiness tended to increase at a steeper rate in the caffeine and placebo groups during the first 36-40 hours without sleep. Again, few differences were seen between the four groups following 68 hours without sleep. The placebo group seemed to experience the most recovery in mood following the 2 hour nap. Most mood measures in the placebo group moved toward the levels reported prior to sleep loss. This was often not the case in the dextroamphetamine and modafinil groups. In several instances involving the Profile of Mood States (POMS) or the Visual Analog Scale (VAS), the baseline adjusted pre-nap reports of increased fatigue and sleepiness or decreased energy and vigor continued after the nap (figures 8 and 9). The caffeine group showed mixed results following the nap, with some recovery on the measures of fatigue, jitteriness and tension, but not vigor, confusion or alertness. Caffeine is known to produce mixed results on mood. Some researchers have reported positive effects (De Valck et al., 2003; Rogers et al., 2003) some have reported negative effects (Childs & de Wit, 2006) and others find no effects on mood states (Hewlett & Smith, 2006; Leiberman et al., 1987). Differences in methodologies such as subject population choice (light caffeine user, heavy users in withdrawal, or caffeine non-users), caffeine dose, and deprivation lengths can easily account for the mixed results. However, it seems reasonable that any of these drugs will at the least weaken psychological recovery normally produced by naps.

While mood during sleep deprivation suffered in all drug groups in comparison to baseline, it was clear that volunteers in the dextroamphetamine and modafinil groups were feeling less fatigued and irritable, and more vigorous, than the placebo and caffeine groups. The data also revealed that modafinil tended to preserve talkativeness at slightly above baseline levels throughout the entire 68 hours without sleep. While not all measures attained statistical significance, trends in this data are in agreement with many others who have examined the ability of stimulants to mitigate fatigue-induced mood declines (Baranski et al., 2004; Caldwell et al., 1999a; 2004; Turner et al., 2002). Virtually all measures on the POMS and VAS returned to baseline in the placebo, dextroamphetamine, and modafinil groups and in some cases exceeded baseline levels (talkativeness, energy, and alertness) following the 10 hours of recovery sleep. However, the caffeine group continued to report higher levels of fatigue and lower levels of alertness and vigor than the other groups.

Sleep

Only one group difference was found among the four treatment groups on the RTSW, an objective measure of alertness. Volunteers in the dextroamphetamine group were generally able to stay awake longer (average about 6 ½ min) during the deprivation period than those in the placebo group (<2 min) (figure 4). The caffeine and modafinil groups were not statistically different from the placebo group. While an estimated 30-40% of dextroamphetamine and modafinil were bio-available at the time scheduled for the nap, volunteers had little trouble

falling asleep after 68 hours of continuous wakefulness. No differences were seen in the amounts of time that the groups spent in stage 1 or stage 2 sleep. However, the dextroamphetamine group and the modafinil group showed opposite patterns of SWS and REM sleep. Subjects in the dextroamphetamine group spent the most time in SWS and the least amount of time in REM while the modafinil volunteers spent the least amount of time in SWS and the most amount of time in REM. The placebo and caffeine groups spent a similar amount of time in each stage of sleep. As expected, subjects had no trouble falling asleep or staying asleep during the 10-hour sleep recovery period provided. When compared to baseline levels, all groups spent less time in stage 1 and more time in SWS and REM obtaining restorative sleep. However, the caffeine group did not display the same level of increased REM as was seen in the other groups. This may explain why the caffeine group continued to report higher levels of fatigue and lower levels of alertness and vigor than the other groups despite 10 hours of sleep.

Performance tests

None of the reaction time measures (PVT, RTI simple, and RTI five choice; figures 15 and 16) were significantly influenced by drug administration. However, all three measures did show significant session effects, indicating that they were capturing fatigue-induced increases in reaction time. Similar results were seen of the MTS and the SOC. Both of these tests recorded declines in performance with increased amounts of fatigue, but neither was influenced by drug administration. The only CANTAB subtest to detect group differences on several measures was the RVP (rapid visual information processing test; figure 18). This test detected group differences in response patterns on 4 of the 6 measures. All main effects were produced by poorer performance on the part of the placebo group than all three of the drug groups. As with the other cognitive and performance tests, the WOMBAT showed few drug main effects for drug condition. There were several session by drug interactions on the individual portion of the WOMBAT as well as the dual (duo) portion of the task (figure 20). In most instances, these differences were due to better performance on the part of the dextroamphetamine group (figure 22). In general, none of the cognitive or reaction time tests showed clear superiority for any of the drug treatments. Of the seven flight maneuvers conducted in the UH-60 simulator, there were main effects for drug on two of the measures during the 68 hour deprivation period. One main effect was due to superior performance by the modafinil group on the hover maneuver, the other was due to superior performance of the dextroamphetamine group on the climb maneuver (figure 23). No session or session drug effects were observed throughout the entire test period.

It is apparent from the results of the reaction time, cognitive tests, and flight testing that variability within the groups was quite high. One explanation might be that the experimental design resulted in insufficient power. The nap/sleep portion of the design introduced a confounding factor that effectively precluded those data from being included with the analysis of drug effects. In this repeated measures design, the net result was fewer observations per participant than originally planned. A retrospective power analysis of the data obtained during this study revealed that where significant effects were found, the effect size (Omega-squared) was large and statistical power (1-ß) was sufficient to detect differences in the recorded data. However, this analysis also indicated that many of the measures yielded only small to moderate effect sizes, and the power in those instances was likely insufficient to detect the effects

(assuming they were real). This Type II error must be considered both in the context of the current study (e.g., the possibility of erroneously concluding a lack of effect) and in the context of future research employing these measures (e.g., adjusting sample size to ensure sufficient power for a variety of measures).

Retrospective study comparisons

The comparison of data from studies conducted using similar paradigms produced few significant results. POMS and VAS questionnaires were administered in all these studies. In general, these data suggest that the lower dose groups reported less tension and irritability, and for the modafinil comparisons, the lower dose group reported more energy than the higher dose group at comparable levels of sleep deprivation. Comparisons also showed that pilots given twice as much dextroamphetamine as the group in our study did not show significantly better performance throughout the testing period (the initial 40 hours of sleep deprivation in these studies). The high dose dextroamphetamine group was superior only on the hover flight maneuver scores. The lower dose of modafinil used in this study did tend to produce superior, but not significantly so, results on all flight maneuvers when compared to pilots given the higher doses. Since it is unlikely that the lower doses of dextroamphetamine or modafinil were behaviorally equivalent (or superior) to the higher doses, the most plausible explanation for these results may be the fact that volunteers in our study were run in pairs. Several of the researchers, technicians, and research aviators who have worked on these USAARL studies, noted that volunteers, when run in pairs, were more social, more agreeable, and less apt to express any discomfort or complain than subjects being run singly. Despite a longer duration of sleep deprivation (68 hours+17 hours post nap) in the present study, and drug dosages that were half of those previously used, our volunteers continued to interact with their co-pilot, the research aviators, and the research staff with no loss of temper or social withdrawal as had been seen in previous studies. The psychosocial environment undoubtedly has dramatic effects on cognition and flight performance during periods of sleep deprivation, and cannot be overlooked.

Summary and conclusions

While a considerable amount of research has been conducted on the use of stimulants or napping as countermeasures for performance declines in aviators due to sustained operations, the effects of the combination of these countermeasures has not been examined. This study examined the combined effects of stimulants with napping. While none of the drug treatments were able to stave off mood and performance declines throughout the entire period of drug testing (68 hours), results from this study showed several fairly clear trends. In most instances, the dextroamphetamine and modafinil groups were superior to the placebo and caffeine groups. It was also clear that a 2-hour nap was not sufficient to return performance to anything approaching baseline levels. It is possible that some short-term benefits resulted from the nap but were missed since in some cases it could have been up to an hour post-nap before measurements were taken due to scheduling limitations. The nap did seem to improve performance in the placebo group but not in the drug groups implying that drug treatments and naps are not effectively synergistic. Despite the lengthy deprivation period, 10 hours of recovery

sleep following the expected washout time for the drugs was sufficient to ameliorate the vast majority of the fatigue-related mood changes and performance impairments.

Overall, several important conclusions can be drawn from these results. First, modafinil, at these doses, did not produce any side effects that would be of aeromedical concern. However, a high dose of caffeine did produce side effects that could be of concern for both the aeromedical and ground communities. Second, the effects of modafinil and dextroamphetamine on measures of mood and performance were quite similar. Third, but no less important, comparison of data from studies conducted using similar paradigms showed that pilots given twice as much drug as the group in our study did not differ significantly (on performance measures that were comparable) throughout the first 40 hours of sleep deprivation.

When compared to previous flight simulator studies of dextroamphetamine and modafinil, the two doses of dextroamphetamine and modafinil were similar in efficacy (in terms of their effects on operator performance). This relative lack of drug and time-related effects on flight performance was surprising. Only two of eight flight maneuvers demonstrated any effect, and those two effects did not point to a consistent effect of drug condition or testing time. It seems possible that the new element of crew interaction during the simulated flight profiles may have injected an element of stimulation and excitement which was missing in previous single-subject/pilot research flights (Caldwell et al, 1994). Retrospective scoring of verbal interactions may reveal differences in the drug groups since the task requirements may have led to differential compensatory behaviors in the teams. The psychosocial effects of having another aviator in the next seat who performed the duties of copilot, colleague, alertness monitor, etc., almost surely affected in-flight performance. On the one hand, this makes it difficult to assess the 'worst case' fatigue scenario and the response to these pharmacological countermeasures; on the other hand, aircrew operate as teams in the 'real world,' making this study more representative of the milieu in which fatigue countermeasures may be needed.

Nevertheless, these drugs maintained decision making, cognitive functioning, judgment and situational awareness, relative to placebo. Those capabilities, along with crew resource management, were sustained just as well in two-man crews as previously demonstrated in studies of individual aircrew performance, and at lower doses. These findings strongly suggest that stimulant medications can assist the warfighter in maintaining acceptable levels of judgment and decision making, as well as crew coordination, when combat requirements dictate long periods of sleep deprivation. A subsequent study using the same lower doses of modafinil and dextroamphetamine in the in-flight environment (e.g., actual helicopter) is currently underway at the USAARL. This in-flight study includes non-aviation tasks of military relevance, and will answer lingering questions regarding the suitability of modafinil for use by the operational community.

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APPENDIX A

Significance Table

Physiological Tests	Measure	Drug Analysis			Nap Analysis		
		Drug	Session	DxS	Drug	Session	DxS
Pupilometry	Pupil Diameter- Minimum	p<0.001	NS	NS	NS	p<0.002	NS
	Pupil Diameter- Maximum	p<0.001	NS	NS	NS	NS	NS
	Constriction Latency	NS	NS	NS	NS	NS	NS
	Maximum Constriction Velocity	NS	NS	NS	NS	NS	NS
	Constriction Velocity	NS	NS	NS	NS	NS	NS
	Dilation Velocity	NS	NS	NS	NS	NS	NS
Vital Signs	Oral Temperature	NS	p<0.001	p<0.017	NS	p<0.001	NS
	Systolic Blood Pressure	NS	p<0.007	NS	NS	p<0.001	NS
	Diastolic Blood Pressure	NS	NS	p<0.078	NS	p<0.073	NS
	Heart Rate	p<0.001	p<0.001	NS	NS	p<0.001	NS
RTSW	Sleep Latency	p<0.042	p<0.001	NS	NS	p<0.001	NS
NAP	Stage 1 Sleep	NS	NA	NA	NA	NA	NA
	Stage 2 Sleep	NS	NA	NA	NA	NA	NA
	Slow Wave Sleep	p<0.040	NA	NA	NA	NA	NA
	REM	p<0.050	NA	NA	NA	NA	NA
Recovery Sleep	Stage 1 Sleep	NS	NA	NA	NA	NA	NA
	Stage 2 Sleep	NS	NA	NA	NA	NA	NA
	Slow Wave Sleep	NS	NA	NA	NA	NA	NA
	REM	p<0.041	NA	NA	NA	NA	NA
Questionnaires							
POMS	Fatigue	p<0.013	p<0.001	NS	NS	p<0.001	p<0.001
	Tension	NS	p<0.013	NS	NS	p<0.001	NS

	Anger	NS	NS	NS	NS	NS	NS
	Depression	NS	p<0.028	NS	NS	NS	p<0.013
	Vigor	NS	p<0.001	NS	NS	p<0.001	NS
	Confusion	NS	p<0.001	NS	NS	p<0.001	NS
VAS	Alertness	p<0.009	p<0.001	NS	NS	p<0.001	NS
	Irritability	p<0.045	NS	NS	NS	p<0.017	NS
	Sleepiness	p<0.033	p<0.001	p<0.002	NS	p<0.001	NS
	Talkativeness	p<0.011	NS	NS	p<0.028	p<0.001	p<0.015
	Energy	NS	p<0.001	NS	NS	p<0.001	NS
	Confidence	NS	p<0.001	NS	NS	p<0.001	NS
	Jitteriness	NS	p<0.029	NS	NS	p<0.006	NS
	Anxiousness	NS	NS	NS	NS	NS	NS
SSQ	Nausea	p<0.034	p<0.024	NS	NS	p<0.001	NS
	Visuomotor/eyestrain	p<0.018	p<0.001	NS	NS	p<0.001	p<0.045
	Disorientation	NS	p<0.001	NS	NS	p<0.001	NS
	Total Symptom Severity	p<0.026	p<0.001	NS	NS	p<0.001	NS
Questionnaires	Measure	Drug Analysis			Nap Analysis		
		Drug	Session	DxS	Drug	Session	DxS
Symptom Checklist	Nausea	p<0.001	NA	NA	NA	NA	NA
	Jitteriness	p<0.024	NA	NA	NA	NA	NA
	Nervousness	p<0.005	NA	NA	NA	NA	NA
	Excitation	NS	NA	NA	NA	NA	NA
	Anger	NS	NA	NA	NA	NA	NA
	Headache	NS	NA	NA	NA	NA	NA
	Happiness	NS	NA	NA	NA	NA	NA
	Stomach pain	NS	NA	NA	NA	NA	NA
	Dry mouth	NS	NA	NA	NA	NA	NA
	Pounding heart	NS	NA	NA	NA	NA	NA
	Racing heartbeat	NS	NA	NA	NA	NA	NA
Performance Tests							
PVT	Reaction time	NS	p<0.003	NS	NS	p<0.004	NS

CANTAB – RTI	Simple Reaction Time	NS	p<0.001	NS	NS	p<0.035	NS
	Simple Movement Time	NS	p<0.006	NS	NS	p<0.002	NS
	5-choice Reaction Time	NS	p<0.001	NS	NS	p<0.001	NS
	5-choice Movement Time	NS	p<0.022	NS	NS	p<0.001	NS
MTS	Percent Correct	NS	NS	NS	NS	NS	NS
	Latency	NS	p<0.006	NS	NS	p<0.0001	p<0.006
RVP	Hits	p<0.001	p<0.001	NS	p<0.047	p<0.001	NS
	Misses	p<0.001	p<0.001	NS	NS	p<0.001	NS
	Correct Rejections	p<0.006	p<0.001	NS	NS	p<0.001	NS
	A'	p<0.001	p<0.001	NS	p<0.037	p<0.001	NS
SOC	Problem Solved Min Moves	NS	p<0.012	NS	NS	p<0.003	NS
WOMBAT (single)	3-D Figure Rotation	NS	NS	NS	NS	NS	p<0.047
	Quadrant Location	NS	NS	NS	NS	p<0.020	p<0.015
	Digit Cancellation	NS	NS	p<0.001	p<0.042	NS	NS
Duo WOMBAT	Tracking	NS	NS	p<0.001	NS	NS	p<0.032
	3-D Figure Rotation	NS	NS	p<0.023	NS	NS	NS
	Quadrant Location	NS	NS	NS	NS	NS	p<0.023
	Digit Cancellation	NS	NS	NS	NS	NS	p<0.001
Flight Simulator	Hover	p<0.011	NS	NS	NS	NS	NS
	Straight & Level	NS	NS	NS	NS	NS	NS
	CR Turn VMC	NS	NS	NS	NS	NS	NS
	Climb	p<0.018	NS	NS	NS	NS	NS
	CR Turn IMC	NS	NS	NS	NS	NS	NS
	SL IMC	NS	NS	NS	NS	NS	NS
	ILS Approach	NS	NS	NS	NS	NS	NS

Questionnaires	Measure		Drug Analysis			Nap Analysis	
		Drug	Session	DxS	Drug	Session	DxS
POMS	Fatigue	p<0.013	p<0.0001	NS	NS	p<0.0001	p<0.0001
	Tension	NS	p<0.013	NS	NS	p<0.0001	NS
	Anger	NS	NS	NS	NS	NS	NS
	Depression	NS	p<0.028	NS	NS	NS	p<0.013
	Vigor	NS	p<0.0001	NS	NS	p<0.0001	NS
	Confusion	NS	p<0.0001	NS	NS	p<0.0001	NS
VAS	Alertness	p<0.009	p<0.0001	NS	NS	p<0.0001	NS
	Irritability	p<0.045	NS	NS	NS	p<0.017	NS
	Sleepiness	p<0.033	p<0.0001	p<0.002	NS	p<0.0001	NS
	Talkativeness	p<0.011	NS	NS	p<0.028	p<0.0001	p<0.015
	Energy	NS	p<0.0001	NS	NS	p<0.0001	NS
	Confidence	NS	p<0.0001	NS	NS	p<0.0001	NS
	Jitteriness	NS	p<0.0299	NS	NS	p<0.006	NS
	Anxiousness	NS	NS	NS	NS	NS	NS
SSQ	Nausea	p<0.034	p<0.024	NS	NS	p<0.0001	NS
	Visuomotor/eyestrain	p<0.018	p<0.0001	NS	NS	p<0.0001	p<0.045
	Disorientation	NS	p<0.0001	NS	NS	p<0.0001	NS
	Total Symptom Severity	p<0.026	p<0.0001	NS	NS	p<0.0001	NS
Symptom Checklist	Nausea	p<0.001	NA	NA	NA	NA	NA
	Jitteriness	p<0.024	NA	NA	NA	NA	NA
	Nervousness	p<0.005	NA	NA	NA	NA	NA
	Excitation	NS	NA	NA	NA	NA	NA
	Anger	NS	NA	NA	NA	NA	NA
	Headache	NS	NA	NA	NA	NA	NA
	Happiness	NS	NA	NA	NA	NA	NA
	Stomach pain	NS	NA	NA	NA	NA	NA
	Dry mouth	NS	NA	NA	NA	NA	NA
	Pounding heart	NS	NA	NA	NA	NA	NA
	Racing heartbeat	NS	NA	NA	NA	NA	NA

DEPARTMENT OF THE ARMY
U.S. Army Aeromedical Research Laboratory
Fort Rucker, Alabama 36362-0577